University of Alberta

Neuroendocrine Changes in Critically Ill Children: The Natural History of Nonthyroidal Illness Syndrome in Children Who Have Undergone Cardiac Bypass Surgery

by

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DEDICATION

This thesis is dedicated to my mother, Paula Marks, who passed away in the midst of my studies. She was a wonderful mother and an equally wonderful educator. Any grammatical errors in this paper need to be excused as it was not proofread and red penned by "Perfect Paula". She was always proud of all my accomplishments.

ABSTRACT

This study examined the hypothalamic-pituitary-thyroid axis changes in children undergoing cardiac surgery. Thyroid function was measured in 21 children and compared to markers of clinical outcome and illness severity.

All patients exhibited nonthyroidal illness syndrome (NTIS). Total T3 (TT3), free T3 index (FT3I), free T4 (FT4), and thyrotropin (TSH) decreased postoperatively while reverse T3 (RT3) and T3 uptake (T3U) increased. TT3, FT3I, and T3U still differed from preoperative levels after 8 days. Certain clinical parameters including dopamine use, corticosteroid use, type of surgery, weight, age, and intraoperative temperature influenced the degree of NTIS. Thyroid hormone changes correlated with clinical outcomes and illness severity. Early hormone changes were predictive of clinical outcome.

NTIS was present in this model of critical illness in children. The degree of NTIS was related to, and possibly predictive of, clinical outcome and illness severity.

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LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone (corticotropin)
Alb	albumin
AMP	adenosine monophosphate
APACHE	acute physiology and chronic health evaluation
ASD	atrial septal defect
ATP	adenosine triphosphate
AV	aortic valve
C	celcius
CI	confidence interval
CPB	cardiopulmonary bypass
CRH	corticotropin releasing hormone
CV	coefficient of variation
D1	deiodinase type 1
D2	deiodinase type 2
D3	deiodinase type 3
DHCA	deep hypothermic arrest
ESS	euthyroid sick syndrome
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT3I	free triiodothyronine index

FT4	free T4 (thyroxine)
GH	growth hormone
GHRH	growth-hormone releasing hormone
GnRH	gonadotropin releasing factor
ICC	interclass correlation coefficient
ICU	intensive care unit
IL-1	interleukin-1
IL-6	interleukin 6
kg	kilograms
LH	lutenizing hormone
LHRH	lutenizing hormone releasing hormone
l-thyroxine	levothyroxine
mcg/dl	micrograms per deciliter
mRNA	messenger ribonucleic acid
mU/L	milliunits per liter
μU/ml	microunits per milliliter
ng/dl	nanograms per deciliter
nmol/L	nanomoles per liter
NTIS	nonthyroidal illness
OR	odds ratio
PA	pulmonary artery
PAC	preassessment clinic
PELOD	pediatric logistic organ dysfunction

PICU	pediatric intensive care unit
pmol/L	picomoles per liter
POD	postoperative day
PRL	prolactin
RR	relative risk
RT3	reverse T3
RV	right ventricle
RVOTO	right ventricular outflow tract obstruction
SD	standard deviation
SE	standard error
SES	sick euthyroid syndrome
T2	diiodothyronine
T3	triiodothyronine
T3U	triiodothyronine uptake
T4	thyroxine
TBG	thyroid binding globulin
TBPA	thyroxine binding prealbumin
TISS	therapeutic index score system
TNF	tumour necrosis factor
TRH	thyrotropin releasing hormone
TSH	thyroid stimulating hormone (thyrotropin)
TT3	total triiodothyronine
TT4	total thyroxine

VSD ventricular septal defect

CHAPTER 1: INTRODUCTION

1.0 Background

The term neuroendocrine refers to the interactions that occur between the brain and the endocrine system. The main neuroendocrine interfaces are the hypothalamic – pituitary – peripheral endocrine glands axes. Physiological stress can result in neuroendocrine changes in humans. Various neuroendocrine changes have been described in critically ill patients, the ultimate example of physiological stress. These changes involve alterations in the levels and pulsatility of the hypothalamic and pituitary signalling hormones and the peripheral circulating hormones.

Neuroendocrine changes in the hypothalamic-pituitary-thyroid axis result in nonthyroidal illness syndrome (NTIS) characterized by abnormal thyrotropin (TSH) and thyroid hormone levels. Other neuroendocrine changes involving other hypothalamic-pituitary axes that may occur in the setting of critical illness include increased serum cortisol levels [121 138], insulin resistance [115 145], altered growth hormone (GH) secretion [88 111 140], altered prolactin (PRL) secretion [88], and decreased serum testosterone. [38 133 135 136 143 146] It is not clear whether, in the setting of illness, these changes are beneficial and promote recovery and are therefore adaptive, or if they are rather a direct result or cause of the illness and associated organ failures and are therefore maladaptive. [25 32 131 135] It has been proposed that in the acute phase of illness these changes may be adaptive, but

without recovery and then the onset of a prolonged illness they become maladaptive. [131 135]

In adults, there has been some suggestion that NTIS and other neuroendocrine changes in critical illness may adversely affect outcome. This has led to proposals for use of hormonal intervention to improve outcome. This approach is controversial. [32 123] There is little data assessing neuroendocrine changes in critical illness and its effect on outcome in children. The purpose of this study was to determine the natural history of the neuroendocrine changes affecting the hypothalamic-pituitary-thyroid axis, or NTIS, in children who have undergone cardiac bypass surgery, a unique and somewhat homogeneous example of critical illness, and to correlate these changes with outcome.

1.1 The Normal Hypothalamic-Pituitary Axes

The hypothalamus, pituitary and peripheral endocrine glands regulate hormone secretions through a series of complex feedback mechanisms. The hypothalamus secretes hormones, referred to as releasing factors, which signal the anterior pituitary gland to release stimulating hormones. These stimulating hormones, in turn, lead to peripheral hormone secretion from specifically targeted endocrine glands. The hypothalamus also secretes inhibiting factors which are also involved in regulating pituitary hormone secretion. Each hypothalamus-pituitary-endocrine gland axis is regulated by positive and negative feedback effects on both the hypothalamus and pituitary. The hypothalamus produced releasing factors include

thyrotropin - releasing hormone (TRH), corticotropin - releasing hormone (CRH), growth hormone - releasing hormone (GHRH), and lutenizing hormone - releasing hormone (LHRH). The inhibiting factors released by the hypothalamus include dopamine, which has its main effects in inhibiting PRL and TSH secretion, and somatostatin which inhibits GH secretion. The hypothalamic releasing and inhibiting hormones control the anterior pituitary secretion of the stimulating hormones TSH, corticotropin (ACTH), GH, lutenizing hormone (LH), follicle-stimulating hormone (FSH), and PRL.

1.2 Normal Thyroid Function

TSH secretion from the anterior pituitary is regulated by TRH secreted from the hypothalamus, and also via feedback from circulating thyroid hormone levels. TRH stimulates TSH release from the anterior pituitary gland. Somatostatin and dopamine, also secreted from the hypothalamus, both inhibit TSH secretion. [126] Thyroid hormones, mainly triiodothyronine (T3), negatively feedback to both the hypothalamus and pituitary to inhibit TRH and TSH secretion.

TSH stimulates thyroid gland production and release of the thyroid hormones thyroxine (T4) and, to a lesser extent, T3. The TSH receptor in the thyroid cells is part of the G – protein coupled seven transmembrane domain family of receptors. TSH receptor binding activates adenylate cyclase and results in increased cyclic AMP levels. Cyclic AMP then activates protein kinase-A which leads to protein phosphorylation within the thyroid cells. These proteins regulate thyroid cell

function and, under the influence of TSH, stimulate increased follicular epithelium height and increased iodide transport, thyroglobulin synthesis, iodotyrosine and iodothyronine formation, thyroglobulin proteolysis, and T4 and T3 secretion. [126] T4 and T3 are formed by iodination of thyroglobulin tyrosyl residues.

TSH is secreted in a pulsatile fashion and with a circadian rhythm. Its levels are lower during the day and peak through the night. [18 45] Generally, the TSH pulse frequency and amplitude is increased between 2000 and 0400 hours. [18] The physiological importance of this nocturnal surge is unclear as the T4 and T3 levels are not increased with the elevated TSH levels. [45] The amplitude of the TSH pulse is also decreased with fasting, surgery, illness, and early onset of sleep. [1 7 18 107] While most studies have shown that the pulse frequency is unaffected by these conditions, some studies have illustrated contrasting results. [108]

T4 and T3, in smaller concentrations, are both released from the thyroid gland. T3 is the biologically active form of thyroid hormone. T4 conversion to T3 by monodeiodination in peripheral tissues is responsible for about 80% of the T3 production. There are three known deiodinase enzymes involved in thyroid hormone metabolism. Deiodinases types 1 (D1) and 2 (D2) can both convert T4 to T3 by removal of iodine from T4's outer ring. Deiodinase type 3 (D3) can only deiodinate inner ring sites and by doing so deactivates T3 and T4 by converting them to T2 and reverse T3 (RT3), respectively. D1 is also capable of inner ring

deiodination but D3 is thought to be the primary enzyme involved in this reaction. RT3, an inactive metabolite, can be converted to T2 by D1. [59]

D1 is present in the thyroid, liver, kidney, and the central nervous system. D2 is present in brown fat, placenta, skeletal muscle, heart, thyroid, and the central nervous system, including the pituitary. D1 is likely more important than D2 for peripheral conversion of T4 to T3. D2 is thought to be important in T4 to T3 conversion in the pituitary gland, and therefore in feedback to the thyrotrophic cells. D3 activity has been noted in the central nervous system, skin and placenta. [59 61 62] In contrast to expected typical feedback mechanisms, D1 transcription is stimulated by T3. T3 also stimulates D3 activity. D2 activity is stimulated by TSH. D2 transcription and activity is negatively correlated to T3 and T4 levels. [39 52 59 61 70 147] Deiodinase activity can also be affected by non-thyroid hormones such as growth hormone and cortisol. [43]

The serum concentrations of T4, T3 and TSH are normally maintained within a narrow normal range. The pituitary response to TRH and the resulting TSH secretion is very sensitive to small changes in T4 and T3 concentrations. [114 120 128] This sensitive and rapid response of the hypothalamic-pituitary axis maintains normal thyroid function with minimal variation of the serum levels of T4, T3 and TSH.

1.2.1 Physiologic Function of Thyroid Hormones

Thyroid hormone, specifically the bioactive T3, increases the basal metabolic rate, oxygen consumption, and protein synthesis, and also has effects on carbohydrate and lipid metabolism. T3 levels have physiological and clinical consequences on most of the body's systems including the cardiovascular, pulmonary, hematological, gastrointestinal, skeletal, neuromuscular, and sympathetic systems. [62 110] Specifically in regards to the cardiovascular system, T3 increases myocardium contractility, heart rate, and coronary blood flow, improves diastolic relaxation, and decreases afterload. T3 has beneficial effects on calcium transport in the myocyte through the main calcium pathways including the sarcoplasmic reticulum and cell membrane calcium ATPases, and the ATPase independent sodium-calcium exchanger. T3 may also lead to increased catecholamine responsiveness in the myocytes. [110]

1.3 Thyroid Disease

Disorders in thyroid hormone production can result in either overproduction of hormone, known as hyperthyroidism, or underproduction, known as hypothyroidism. The clinical manifestations of either state are a direct result of the effects of low or high thyroid hormone levels on the various physiological systems. For example, the symptoms and signs of hyperthyroidism may include nervousness, heat intolerance, sweating, weight loss, tachycardia, cardiac palpitations, or diarrhea. Conversely, hypothyroidism may present with weakness, cold intolerance, dry skin, weight gain, bradycardia, edema, or constipation.

The most common cause of hyperthyroidism is Graves' disease. Graves' disease is caused by autoantibodies stimulating the thyroid gland and resulting in increased production of thyroid hormone. Therefore, biochemically it is characterized by elevated levels of T3 and T4. TSH levels are low due to the peripheral feedback of the high thyroid hormone levels on the pituitary. The most common cause of hypothyroidism is chronic lymphocytic thyroiditis, also known as Hashimoto's thyroiditis. Like Graves' disease, it is an autoimmune disease with antibody production directed to the thyroid gland. The antibodies in Hashimoto's thyroiditis cause thyroid destruction and blockage of TSH stimulation on the thyroid. Biochemically, primary hypothyroidism is characterized by low levels of T3 and T4 and resulting elevated levels of TSH from decreased thyroid hormone feedback to the central nervous system.

1.4 Neuroendocrine Changes in Critical Illness

Neuroendocrine changes occur in the setting of physiological stress due to various clinical scenarios including starvation, sepsis, surgery, cardiovascular disease, pulmonary disease, renal disease, burns, bone marrow transplantation, and essentially any critical illness. [5 32] However, it is often difficult to separate out starvation as an etiology in some of these scenarios.

Critical illness, like other physiological stresses, leads to a dynamic response of the hypothalamic – pituitary axes. This results in alterations in the absolute levels and pulsatility of the pituitary stimulating hormones and various changes in

peripheral hormone levels. The responses to acute versus chronic critical illness may differ. It is questionable whether these neuroendocrine changes are adaptive or maladaptive in the setting of critical illness, and whether this distinction in fact differs in the acute versus chronic states.

The thyroid, GH, gonadotropin, adrenal and prolactin axes have all been shown to be altered in critical illness. [131 136] For example, in acute critical illness both peak and trough GH levels are elevated and its pulse frequency is increased. [88 111 140] In chronic illness, GH secretion becomes chaotic with overall lower levels, and minimal peaks and pulsatility. [131 136] Prolactin follows a similar pattern as GH with acutely high levels and then low levels with chronicity. [88] In comparison, cortisol generally remains elevated in both the acute and chronic states. [121 138] During acute illness this is accompanied by elevated ACTH levels, while during chronic illness some studies have demonstrated that the ACTH levels become low, therefore implicating a non-ACTH mechanism for the continued increased cortisol levels. [138] Androgen secretion in adult men is decreased during critical illness. In acute illness, this decrease is accompanied by a rise in LH levels. However, in chronic illness there is evidence of hypogonadotropic hypogonadism leading to the low androgen levels. [38 133 143 146] The thyroid hormone changes are complex and further reviewed below. Generally, thyroid hormone levels are low in the acute phase of critical illness and then either rise with clinical recovery or may remain low with chronic illness.

The physiological effects, and possibly benefits, of the various neuroendocrine changes that occur in critical illness require further study but there are some theoretical and proven effects. Elevated cortisol levels may improve hemodynamics, decrease inflammation and, like elevated GH levels, promote the availability of glucose, free fatty acids and amino acids to facilitate recovery. [42 136] Yet interestingly, very elevated cortisol levels have been associated with increased disease severity and mortality [4 121], and a large study showed increased mortality in critically ill adults receiving supplemental growth hormone. [125] Immune function may be improved by elevated prolactin and GH levels. [136] Androgens are anabolic and therefore it can be theorized that their suppression during illness could be beneficial in order to preserve energy and substrate for illness recovery. [136] NTIS and its low thyroid hormone levels may reduce energy expenditure and lessen the catabolic protein breakdown in critical illness.

1.4.1 Non Thyroidal Illness Syndrome (NTIS)

NTIS is also referred to in the literature as sick euthyroid syndrome (SES), euthyroid sick syndrome (ESS), low T3 syndrome, and low T3 – low T4 syndrome. [25] While the latter two names are merely descriptive of the biochemistry, SES and ESS convey a controversial assumption that the thyroid status is normal. [32]

Like other neuroendocrine changes, NTIS can occur with various forms of physiological stress. Other clinical factors that may affect the thyroid function include cardiopulmonary bypass, dopamine, and corticosteroids.

NTIS is characterized by low levels of T3, increased RT3, normal to low T4, and normal to low TSH. The controversy regarding the metabolic status and whether NTIS is adaptive or maladaptive is essentially centered on the inappropriately normal or low TSH levels in the presence of low levels of T3 and T4. This is not consistent with the feedback mechanisms of the normal hypothalamic – pituitary – thyroid axis or primary thyroid disease. NTIS may also result in the loss of the normal nocturnal surge of TSH. [1 108]

CHAPTER 2: REVIEW OF THE LITERATURE

2.0 Overview

A review of the literature reveals a list of studies that have looked at the natural history of neuroendocrine changes during critical illness and possible interventions to modify these changes. The studies on NTIS in particular have fairly consistently revealed the presence of NTIS in critical illness. Many studies have also tried to uncover the pathophysiology behind NTIS. The results of the studies on treatment in NTIS, or in the other neuroendocrine changes, are mixed. The human studies on NTIS generally focus on patients with one of either cardiac disease or other critical illness. The studies can also be divided between those with either adult or pediatric subjects, with much less data available in the latter.

Whether implicitly stated or not, the underlying purpose of all the natural history, pathophysiology, or treatment studies is to determine whether NTIS, or the other neuroendocrine changes, are adaptive or maladaptive. The available literature on the neuroendocrine changes in critical illness is reviewed in the succeeding sections with a major emphasis on the pediatric and NTIS literature.

2.1 NTIS in Adults with Critical Illness

NTIS has been described in various patient settings in adults including starvation, fasting, intensive care, trauma, surgery, sepsis, cardiovascular disease, respiratory disease, burns, malignancy, bone marrow transplant, liver disease, and renal

disease. One study describes NTIS in 251 of 329 inpatients, with a variety of diagnoses. [122]

Many natural history and treatment studies have illustrated NTIS in adults with cardiovascular disease and in those undergoing cardiopulmonary bypass (CPB) surgeries. Bremner and colleagues found low TT3 and FT3 levels, high FT4 levels, and a blunted TSH response in adults undergoing CPB surgery. [19] Robuschi and colleagues also found alterations of thyroid function in a similar population. [106] This group found increased RT3 levels, decreased TT4 and TT3 levels, increased FT4 but, in contrast to Bremner, also increased FT3 levels during CPB. Their population also showed a blunted TSH response to TRH stimulation during CPB. Similar increases in both of the free hormone levels during CPB were found by Gotzsche and Weeke. [44] They theorize that heparin administration during bypass activates lipoprotein lipases resulting in increased levels of non-esterified fatty acids that compete for binding sites with thyroid hormone. This finding is challenged by others who argue that FT3 is irrefutably decreased during CPB. [29 89] This distinction is important as it underlies the decision of whether treatment with supplemental T3 is warranted.

Patients with chronic renal failure have been shown to have low T3 and T4 levels that are not merely explained by thyroid binding globulin (TBG) levels, and also a blunted TSH response to TRH stimulation. [66 97] A study by Maturlo and

colleagues also showed a blunted TSH response in a variety of patients with NTIS. [78] The majority of patients in this study had neoplastic diseases.

NTIS has been compared to severity of illness in some studies involving adult patients. Rothwell and Lawler illustrated that low levels of T4 and TSH, along with elevated cortisol levels, were superior prognostic indicators of mortality than the APACHE II score in their population of critically ill patients. [112] Slag and colleagues found that low T4 levels were highly correlated to mortality in critically ill patients. [119] In burn patients, the degree of NTIS is greater in patients with larger burn sizes and in non survivors. [8] However, an abstract by Lalani and Dhuper describes higher mortality in septic shock patients with normal TSH levels compared to those with suppressed levels. [60] These findings may imply that NTIS is an adaptive protection in those patients that survive.

2.2 NTIS in Children with Critical Illness

The literature on NTIS in children is less vast than that available in adults and the literature that is available on children largely focuses on the population undergoing cardiac surgery for congenital heart lesions. That population is reviewed in depth in the next section (2.2.1). There are a handful of publications describing NTIS in children in non-cardiac surgery settings. [48 53 86 118 127 148]

Zucker studied 27 children, aged 4 months to 16 years, of which 9 were medical ICU patients and the remaining were cardiac surgery patients. [148] Of the 9 medical

patients, 6 had below normal serum T4 and T3 levels, and TSH levels described as < 2.5 μU/ml, at 24 hours after admission to the ICU. No baseline values were done on these patients. Hashimoto and colleagues found low normal T3 levels of less than 1.5 nmol/L, in 13 of 59 outpatients with acute respiratory illnesses. [48] The authors label the 3 patients with T3 levels below 1.2 nmol/l as having NTIS. While a label of NTIS is debatable since the T3 values were still within normal range, the possibility that these non-critically ill outpatients may represent a spectrum of thyroid dysfunction with illness is intriguing. The T3 levels were also found to be inversely proportional to measured interleukin-6 (IL-6) levels in this study.

A few studies in the non-cardiac pediatric population have attempted to correlate thyroid hormone levels to outcome or illness severity. Uzel and Neyzi looked at 13 infants, between 1 month and 12 months of age, presenting with sepsis and/or pneumonia. [127] The study population's initial mean T3 was lower and RT3 was higher compared to healthy controls, and therefore consistent with NTIS. The initial mean T4 and TSH values were not different from the control group. Six of the study patients died and their initial T4 levels seemed to be prognostic. These nonsurvivors' initial T4 values were lower than those in the control group while the initial T4 values in the recovered group did not differ from those in the control group. The survivors group's T3 levels recovered to values comparable to those in the control group while in the nonsurvivors group the T4 and T3 values remained low and did not recover. RT3 values rose and then decreased in both the survivor

and nonsurvivor groups. Simpson and colleagues, like others, illustrated that T3 and T4 levels, but not TSH, were inversely correlated to severity of illness in premature infants. [118] However, as detailed later, thyroid supplementation has not been found to be of benefit in this group.

An abstract publication by Mungan and colleagues further illustrates how the degree of NTIS may be related to illness severity. [86] In this study, TT3, FT3, TT4, and FT4 levels were lower in 21 children with septic shock compared to 51 children with sepsis and 30 controls. In addition, the TT3 and FT3 levels, but not the TT4 or FT4, were lower in the children with sepsis than controls. Twenty-six children died and their TT3, FT3, TT4, and FT4 levels were lower than those in survivors.

However, another study of 26 children with meningococcal sepsis shows some contrasting results to other studies in regards to the possible positive adaptive response of NTIS. [53] In this study by Joosten and colleagues, all patients showed a degree of NTIS but the 8 non-survivors showed "less" NTIS at initial presentation with lower RT3, higher TSH, and higher T3 levels compared to the survivors. Within 48 hours, the survivors showed decreasing levels of RT3 and increasing levels of TSH and T3 compared to their initial levels, but levels were still outside the normal ranges. Many of the same authors of this study published another study on thyroid function in 44 survivors of meningococcal sepsis. [35] Presumably, this study population is a continuation of the previous study. Again, levels were

only measured up to 48 hours after admission. All the children showed low TT3 and high RT3 levels, consistent with NTIS. The TSH levels remained within normal. At admission, the TT3 levels were significantly higher in the short versus long stay group. In addition, changes in TT4, FT4, TT3, RT3, and TSH towards normal levels within the first 24 hours were prognostic and negatively correlated with duration of stay. These hormone changes were also negatively correlated to the IL-6 levels at admission. Long stay children had a decrease in FT4 and RT3 after 24 hours. Of note, 23 children in this study received dopamine which has known effects on thyroid hormone metabolism. The TSH levels were higher in those children who did not receive dopamine and in those who had stopped receiving dopamine. A follow-up publication, again by many of the same authors and again presumably a combination of the previous cohorts, essentially confirmed the results of their previous smaller sample studies. [36] In this study, they now had a total of 69 children with meningococcal sepsis which they analyzed as two separate groups, 45 who did not receive dopamine and 24 treated with dopamine. The 45 in the non-dopamine group consisted of 8 non-survivors, 30 shock survivors, and 7 sepsis survivors. TT4 levels were lower with increased disease severity since the non-survivors had lower levels than survivors, and the shock survivors had lower levels than the sepsis survivors. TT4 was also found to be negatively correlated with other clinical markers of illness severity such as critical illness scores, and IL-6 and lactate levels. RT3 levels were higher in the shock versus sepsis survivors but in contrast they were lower in the non-survivors versus survivors leading to a higher TT3/RT3 ratio in the non-survivors. This is

similar to what the group described in their 2000 publication. [53] The effects of dopamine were similar to their other previous report [35] with dopamine decreasing TSH levels but not affecting TT4, FT4, or TT3 levels. Multivariate analysis showed that higher TT3/RT3 ratios and lower TT4 levels increased the odds for mortality. These two results are somewhat contrasting. When IL-6 was added to the analysis, the thyroid hormone levels were no longer significant and increased IL-6 levels alone greatly increased the odds of mortality. The apparently contrasting results in the non-survivors showing "less" NTIS may be a factor of time. The non survivors may have died prior to there being enough time for them to develop NTIS. Alternatively, the inability of this group to adapt to acute critical illness and develop NTIS may be a factor in their mortality.

2.2.1 NTIS in Children Undergoing Cardiac Surgery

NTIS can occur in neonates or children of any age undergoing a wide variety of cardiac surgeries. There have been a handful of studies that have specifically looked at the presence of NTIS in such children. These studies differ somewhat in their patient selection criteria in regards to age and type of cardiac surgery, and the inclusion of patients with concomitant medications, such as dopamine, or medical conditions, such as Down syndrome, known to affect thyroid function. The studies also differ in the timing and length of the blood sampling period.

The largest study, by Bettendorf and colleagues, studied 132 children undergoing surgery for a variety of congenital heart lesions. [11] The study population was

comprised of neonates and older children, aged 2 days to 16 years. Cardiac bypass was required in the large majority, but not all, of the patients, and the patients had a combination of acyanotic and cyanotic cardiac lesions. Thyroid function was measured preoperatively and then every other day for up to three weeks, however, median period of measurement was for only five days. A degree of NTIS was present in all the patients. The TSH and RT3 changes preceded the T3 and T4 changes. TSH levels reached a nadir on postoperative day (POD) 1 with a 74% decline to a median level of 0.4 mU/L from 1.9 mU/L preoperatively. RT3 rose significantly by 69% also on POD one. T3, T4 and FT4 reached nadir levels on POD 2 with drops of 69%, 58%, and 45%, respectively. The nadirs of T3 and T4 were below the normal range with medians of 0.6 nmol/L and 48.9 nmol/L respectively. The FT4 had a statistically significant drop to 12.9 pmol/L but remained within the normal range. TSH levels recovered to above the baseline preoperative levels on POD five. At the same time, RT3 and FT4 levels also recovered to values statistically insignificant from the preoperative values. T3 and T4 levels were rising by POD 5 but were still below the preoperative levels. The degree of NTIS was worse in those patients who underwent cardiopulmonary bypass (CPB) or received dopamine infusions. The nadirs in the TSH and thyroid hormones were also delayed by one day in those patients who received dopamine. In addition, the TSH recovery levels were higher in these patients. In regards to clinical outcome, this study found that a T3 nadir of less than 0.6 nmol/L was associated with a worse postoperative course. The 52 patients with these lower T3 levels had increased hospital, intensive care, and ventilation days and also

required increased inotropic support compared to the patients with T3 nadir levels equal or above 0.6 nmol/L.

Several smaller studies in children undergoing cardiac surgery similarly showed the presence of NTIS. [3 9 68 72-74 82 87 105 110 113 148] As mentioned previously, Zucker and colleagues followed 27 children, aged 4 months to 16 years, of which 18 underwent cardiac surgery and 9 were patients in the medical ICU. [148] The study period was short and thyroid function was measured for only 24 hours postoperatively in the cardiac surgery patients. Evidence of NTIS was present by 24 hours postoperatively with a decrease in TSH, T4 and T3 levels and a rise in RT3 levels. The mean T3 and T4 levels were already below the normal range by 24 hours. Four of the 18 surgical patients that had RT3 measured had levels above the normal range by 24 hours. Five of the 18 patients received dopamine and 2 were still on an infusion at the time of the 24 hour sample. The authors do not differentiate these patients in their analysis. One of the cardiac surgery patients in this study died. His biochemistry was consistent with NTIS with a T4 of 3.1 mcg/dl (40 nmol/L), T3 25 ng/dl (0.4 nmol/L), TSH < 2.5 μU/ml (< 2.5 mu/L), and RT3 118 ng/dl (1.8 nmol/L). However, 5 of the surviving patients had even lower T4 levels.

Another study illustrated the presence of some aspects of NTIS preoperatively in 20 prepubertal children, mean age 3.6 years, with congenital heart disease. [9] These changes were then worsened by surgery with typical decreases

postoperatively in TT4, TT3, and FT3. FT4 remained normal. The TSH also remained normal in all samples collected. Patients were followed for only 48 hours. This study was unique in that serum binding proteins and thyroid hormone fractions were measured. T4 – binding globulin (TBG) and T4 – binding prealbumin (TBPA), also known as transthyretin, were lower in these patients compared to controls. These differences were already evident preoperatively and did not change significantly postoperatively. Albumin bound T4 (Alb-T4) levels did not differ from controls and also did not change postoperatively. TBG and TBPA bound T4 levels were lower than controls preoperatively and TBG bound T4 then decreased even more so 24 hours postoperatively. Levels of serum TT3, FT3, and TBG bound T3 were also lower than in controls preoperatively. Albumin bound T3 levels were similar to those in controls. All the T3 fractions decreased postoperatively.

Saatvedt and colleagues found typical changes of NTIS in 10 children, aged 23 to 68 months, undergoing elective surgery for congenital heart disease that were followed for a short period postoperatively. [113] Five of the patients had only an atrial septal defect (ASD) defect. T3, FT4 and T4 were measured after induction of anaesthesia, after heparin administration, ten minutes after initiation of CPB, every 30 minutes during CPB, after weaning from CPB, at wound closure, and then at 2, 24, and 48 hours postoperatively. TSH was measured once intraoperatively, at wound closure. The authors elected to "correct" the samples for hemodilution using a mathematical equation adjusting for the change in

hemoglobin concentration. TSH, T3, FT4 and T4 all dropped below baseline levels to nadirs at 24 hours after surgery. FT4 initially increased intraoperatively after initiation of CPB. The T3 and TSH nadirs were delayed by 24 hours in two children who had more complicated cardiac defects, longer CPB and cross clamp times, and more difficult postoperative courses compared to the other 8 patients. One of these children had excess bleeding postoperatively and required repeat surgery. The other child required prolonged ventilation, until POD 3. The remaining cohort was extubated the afternoon following surgery. Both of the children with the more complicated courses also required inotropic support postoperatively while the remainder of the cohort did not.

Murzi and colleagues measured thyroid function in 14 patients, aged 18 months to 14 years, during the CPB procedure, in addition to pre- and postoperatively. [87] Thyroid hormone changes were found to already be present intraoperatively during CPB. NTIS was most severe between 12 to 48 hours postoperatively. The TT3, FT3, and TT4 began to decrease significantly during CPB. TT3 reached a nadir at 36 hours and the FT3 at 48 hours, after surgery. Two hours after surgery the TT4 actually began to improve but then began to decrease again reaching a nadir between 24 to 48 hours after surgery, and then recovered by POD 5. The FT4 remained stable during surgery and immediately postoperatively but then began to decrease at about 6 hours after surgery, reached a nadir at 72 hours after surgery, and recovered by POD five. The TSH increased during anaesthetic induction, came down to baseline during CPB, and reached a nadir between 6 to

12 hours after surgery. The TSH recovered by 72 hours after surgery at the end of POD 2. Similar to the Bettendorf study [11], the TT3 and FT3 still remained below the preoperative values at study end on POD 6. The authors of this study hypothesize as to the possible mechanisms by which CPB itself could affect thyroid function. Based on the non-proportional changes of the TSH, T4 and T3, they conclude that the mechanism is not dilutional. They also noted that the patients had varying degrees of cooling during CPB but this did not seem to be a factor as there was no significant difference in the hormone levels between the normothermic and hypothermic patients. The authors therefore question whether non-pulsatile flow during CPB may blunt the pituitary response to TRH.

A study by Ririe and colleagues looked further into hypothermia during CPB and its effects on the thyroid axis. [105] The study looked at 23 children undergoing CPB during elective repair of a variety of congenital heart lesions. Twelve of the children underwent CPB with only mild to moderate cooling and the remainder underwent CPB with deep hypothermic circulatory arrest (DHCA) down to a median temperature of 18°C. The degree of cooling was not random but dependent on the age of the patient and type of surgery. Therefore, the two groups differed at baseline in regards to type of cardiac lesion, surgical procedure, age, and weight. Seven intraoperative blood samples were collected in addition to samples on POD 1 and POD 2. Both groups showed similar decreases in FT3, FT4, TT3, and TT4 consistent with NTIS. Both groups also had an initial decrease in TSH with the onset of CPB. TSH levels remained low throughout the surgery

in the group undergoing CPB alone. In contrast, the patients undergoing DHCA had a TSH surge through the remaining CPB and surgery period with levels eventually surpassing baseline levels. The authors offer that this TSH surge may be normal and appropriate given the low T3 levels and therefore indicative of an intact hypothalamic-pituitary-thyroid axis preserved by the hypothermia. However, as acknowledged by the authors, the elevated TSH levels could also be a result of pituitary injury. By the morning of POD 1 both groups had similar TSH values.

Mainwaring studied the thyroid effects in a relatively uniform population of 10 neonates, with an average weight of 3.2 kilograms (kg), undergoing CPB surgery for either transposition of the great arteries or total anomalous pulmonary venous drainage. [73] Blood samples were drawn preoperatively, at the start of CPB, and then three times postoperatively with the last sample at POD 5. The CPB prime solution was also analyzed. The FT3 and FT4 were higher in the prime solutions than the preoperative serum values, the TT3 was similar, and the TT4 and TSH were lower in the prime solutions. Serum FT3 and TT3 remained unchanged with CPB initiation, but decreased significantly immediately postoperatively, and then continued to drop within the first 24 hours after surgery. The TT3 was back to baseline by POD 5 and the FT3 had risen considerably but was still below baseline at that point. There was initially a transient rise in FT4 with the initiation of CPB, perhaps due to the prime solution, and then it decreased down to baseline by 1 hour after surgery and then remained unchanged throughout the remainder of

the study period. The TT4 and TSH both decreased with the initiation of CPB and remained at these levels up to 24 hours after surgery. The TT4 returned to baseline at POD 5. The TSH rose to levels almost twice above baseline at POD 5. The exact patterns are difficult to distinguish as there were no samples drawn between 24 hours after surgery and POD 5. In other studies, Mainwaring has attempted to differentiate a thyroid response amongst the various types of congenital cardiac malformations. In one study, he followed the thyroid function in 14 newborns, aged 1 to 12 days old, all with hypoplastic left heart syndrome undergoing first stage Norwood reconstruction. [72] These children all had decreases in FT3 and TT3 levels starting with the initiation of CPB and reaching a nadir at 24 hours after surgery. The levels recovered to preoperative levels on POD 5. In another study, Mainwaring and colleagues compared thyroid function in one group of 8 children undergoing modified Fontan procedures and a control group of 6 children undergoing various other open heart surgeries. [74] Both groups showed evidence of NTIS with decreases in FT3, TT3, FT4, TT4 and TSH postoperatively. However, the FT3, FT4, TT4 and TSH levels returned to baseline levels in the control group by POD 5 but remained below baseline in the Fontan group. The TSH returned to baseline in the Fontan group on POD 8. The FT3, TT3, FT4, TT4 reached nadirs in the Fontan group on POD 5 and were still below baseline on POD 8. Of note, like in other studies, the FT4 did transiently rise during CPB before decreasing. The authors conclude that all children undergoing cardiac surgery have suppression of the pituitary-thyroid axis but NTIS is more

prolonged in children undergoing the Fontan procedure compared to other surgeries.

Like one of the Mainwaring studies, [73], another group specifically looked at infants weighing less than five kg. [82] It is thought that neonates and children of lower weight may respond differently than larger children. Ten infants aged 7 days to 5 months, weighing between 2.8 and 4.7 kg, and undergoing surgery for either transposition of the great arteries, ventricular septal defect, or atrioventricular defect were followed. Blood samples were drawn preoperatively, intraoperatively, and postoperatively up to POD 7. The CPB prime solutions used in six other similar surgeries, but not the specific solutions used with the 10 infants in the study, were analyzed and the TT3, TT4 and TSH levels were much lower than baseline serum levels in the study patients. The authors elected to "correct" the samples taken within 6 hours from the start of CPB for hemodilution using a mathematical equation adjusting for the plasma albumin concentration. TSH, TT3 and TT4 levels decreased intraoperatively and then recovered transiently in the first few hours after surgery. This was followed by another decrease in TT3 and TT4 reaching a nadir at 48 hours. In 7 of the patients, levels returned to normal between POD 5 and 7. After the initial decrease in TSH with the onset of CPB, the levels rapidly surged within 30 minutes to values much above preoperative levels and lasting for about 3 hours. The TSH then decreased rapidly to trough levels at 12 hours, and then began to rise again reaching levels above baseline by POD 3 and peaking on POD 5. As in other studies, TSH

recovery preceded the increases in TT3 and TT4. Two patients that died and one who had a difficult postoperative course showed no recovery in the TT3 and TT4 levels following a nadir between 48 to 72 hours. In these three patients the TSH recovery was present but delayed. The decrease in TT3 and TT4 was less in the five neonates, aged 7 to 19 days, compared to the five older children in the cohort. However, this difference was not statistically significant. Of note, all patients required dopamine postoperatively but the authors do not provide specific details in regards to dose and time, nor is it considered in the analysis.

Both Mitchell and Mainwaring deliberate as to the effect that the CPB prime solution may have on intraoperative thyroid hormone levels. The prime solutions may have concentrations of TSH, T4, and T3 below or above the normal or preoperative baseline serum levels. Theoretically this could at least transiently alter patient serum levels following priming. Mitchell attempts to at least partially explain the thyroid hormone changes in his patients on the dilutional effect of the prime solutions. [81] In response to Mitchell, Mainwaring states that while some changes, like the FT4 levels, may be dilutional, the FT3 changes in his study patients can not be a result of hemodilution based on analysis of the hormone levels in the prime solution used in the study. [73] Mainwaring, like others, implicates many possible factors for the thyroid hormone changes including the deiodinase enzymes, inappropriately decreased TSH secretion, and suppression of the pituitary-thyroid axis possibly secondary to a variety of factors. [76]

Lynch and colleagues report five pediatric cases of thyroid dysfunction following cardiac surgery in patients requiring prolonged chest tube drainage. [68] In four of the five cases the biochemistry is consistent with primary hypothyroidism and not NTIS. The authors hypothesize that the primary hypothyroidism may be a result of the loss of thyroid-binding globulin in the chest tube drainage. Minimal biochemistry is available in the publication but the one remaining case reported may in fact be consistent with NTIS. In this case, the TSH was 0.6 mU/L and FT4 was 0.72 ng/dl (9.3 pmol/L) on POD 17. The patient had a chest tube at this time but her severity of illness is not described in detail. L-Thyroxine replacement was initiated and TSH and FT4 levels apparently remained within the normal range while on treatment. Of interest, the TSH rose up to 7.42 mU/L following discontinuation of the L-thyroxine on POD 114 but did eventually returned to normal without treatment.

One small study in pediatric patients attempts to compare thyroid function and illness severity. In this study, Allen and colleagues followed the thyroid function in 12 children, aged 1 month to 9 years, undergoing cardiac surgery. [3] Thyroid function was measured preoperatively and then on five more occasions up to 72 hours after surgery. Three of the patients were on dopamine infusion at the time the blood samples were drawn and three of the patients had Down syndrome. All the patients had evidence of NTIS. T3 levels decreased 35% from baseline and reached a nadir of 0.71 nmol/L 24 hours after surgery and then did not improve significantly throughout the study's remaining observation period. Six patients

had very low T3 levels, as defined by the authors as a level below 0.46 nmol/L. RT3 levels rose dramatically at 12 hours after surgery and then returned to baseline levels at 72 hours. T4 levels were at their nadir of 71 nmol/L at the study end of 72 hours. TSH levels were normal at 72 hours after surgery. It is unclear from the publication how the TSH values differed from baseline. One of the patients with Down syndrome had one elevated TSH level of 12 mU/L, postoperatively. Illness severity was measured in this study using a modified Therapeutic Intervention Scoring System (TISS) score. [30] Through regression analysis, TISS scores had a correlation coefficient of -0.63 +/- 0.17 with T3 levels, and 0.51 +/- 0.18 with RT3 levels. Changes in illness severity preceded changes in thyroid function. This time frame relation led the authors to conclude that the thyroid function changes were not the cause of increased illness severity, but rather resulted from the critical illness.

This section has reviewed the handful of studies published describing the presence and natural history of NTIS in children who have undergone cardiac surgery. The studies illustrate that most of these children have the biochemical changes consistent with NTIS. There is some variation in the natural history and time course depicted amongst the studies. The TSH nadir was usually early in the postoperative period with a range from POD 0 to 1 in the various studies. The timing of the TSH recovery was quite varied between the studies and ranged from POD 2 to 5, and was on POD 8 in the small study with 8 patients undergoing the Fontan procedure [74]. The timing of the T3, T4, FT3, and FT4 nadirs were either

on POD 1 or 2 for most of the studies. However, the study of the Fontan patients [74] showed later T3, T4, FT3, and FT4 nadirs on POD 5. That same study illustrated that the thyroid hormones had not yet recovered by POD 8. Some studies showed thyroid hormone recovery on POD 5 or 6 while some others showed levels still below baseline at that time. The remaining studies did not follow the hormone levels long enough to comment on this. A few of the studies did nicely illustrate that the TSH and RT3 recoveries preceded the recoveries of the other thyroid hormones. [11 82] Only a few of the studies followed FT3 levels. RT3 was also only followed by a few studies. The studies that did found a peak on either POD 0 or 1 and a recovery on POD 3 or 5.

The available data on NTIS in this population of children is still rather limited. There is the one large study of 132 patients although 48 of these patients were under one year of age and not all the patients required CPB. [11] The remaining studies' sample sizes ranged from 8 to 23 patients with the 3 largest studies measuring the thyroid function for only 24 or 48 hours. The studies' time periods ranged from 1 to 9 days. The study with the longest time period only had a sample of 8 patients. In addition, there are some wide time gaps between hormone measurements in some of the studies. Therefore, a detailed description of the natural course is difficult in those studies. Most of the patients in the various studies underwent CPB surgery but there were some patients included in the studies that did not. The presence or absence of CPB is likely an important

distinction to make when studying NTIS. Some of the studies also include patients with less severe congenital lesions such as ASDs.

Only two of the studies compared the course of NTIS to clinical markers of illness severity. [3 11] Only one of these studies used a critical illness scoring scale. In that small study of 12 patients thyroid function was followed for only 72 hours. [3]

The studies to date in children undergoing cardiac surgery leave some unanswered questions regarding the natural history of NTIS. Many of the studies have heterogeneous populations, infrequent and short duration of sampling, incomplete hormone profiles, and lack of comparison to illness severity and outcome. The objective of my study was to look at a homogenous population with frequent sampling of full thyroid profiles including TSH, TT3, FT3I, T3 uptake (T3U), FT4 and RT3 for up to 8 days following surgery. My study will also aim to compare the NTIS changes to illness severity and a critical illness scoring scale, the Pediatric Logistic Organ Dysfunction (PELOD) score [64]

2.3 The Pathophysiology of NTIS

As described, patients with NTIS have decreased serum levels of TT3 and FT3 along with increased RT3 within hours of illness onset or surgery. With severe illness the serum T4 level also decreases. These serum changes have been correlated with peripheral tissue hormone levels. [100]

Altered activity of the iodothyronine deiodinases, D1, D2 and D3, has long been described as a major contributor in the pathophysiology of NTIS. [54] The functions and locations of the deiodinases are described in chapter 1. In the healthy individual, D1 is thought to be the major deiodinase and converts T4 to T3 and metabolizes RT3 to T2. In NTIS, it is believed that D1 activity is decreased while D3 activity is increased. This would neatly explain the elevated RT3 and low T4 and T3 levels found in NTIS. This theory was supported in a study by Peeters and colleagues looking at post mortem blood, liver, and skeletal samples of 80 ICU patients. [101] Their findings showed that D1 activity in the liver was down regulated, and D3 activity in the liver and skeletal muscle, areas where D3 is usually not present in healthy individuals, was up regulated. The D1 activity was positively correlated with the T3/RT3 ratios. The D3 activity was negatively correlated with this ratio but this did not reach statistical significance. The decreased D1 activity was supported in a follow-up publication showing elevated T4-sulfate levels in this same population. [99] An in vivo study in rabbits by Van den Berghe's group, confirmed the down regulation of D1 and the up regulation of D3 in NTIS. [34] This study also found that D1 activity improved with TRH infusion. The D3 activity also normalized with TRH infusion but the addition of GH-releasing peptide-2 was required in order to normalize the RT3 levels. The authors conclude that these findings imply that D1 is suppressed by changes in the thyrotropic axis only but D3 is upregulated by changes in both the thyrotropic and somatotropic axes. Others have suggested that down regulation of D2 activity in peripheral tissue is a major factor causing decreased T3 levels in NTIS [70].

However, in a recent publication, Mebis and colleagues found that D2 was not altered in acute critical illness compared to controls and in fact was upregulated in prolonged illness and inversely correlated to T3 levels. [80]

The inappropriately normal TSH levels in the presence of low thyroid hormones in NTIS point to a possible central etiology of NTIS with an alteration in the hypothalamic – pituitary axis. Post mortem studies do show small thyroid glands in previously chronically ill patients. [33] Alteration in the axis is also evident by the decrease in TSH pulsatility and loss of the nocturnal TSH surge and circadian rhythm. [19 106] Bartalena illustrated the loss of the nocturnal TSH surge for 5 nights in 10 surgical patients with NTIS. [7] Romijn found an absent nocturnal TSH surge in 15 of 26 medical patients with NTIS. [108] Two of the 11 patients with a preserved TSH surge died while 8 of the 15 without a TSH surge died. This difference in mortality did not reach statistical significance. A post mortem study by Fliers and colleagues further implicates a central etiology in the pathophysiology of NTIS. [41] In this interesting study they measured in situ TRH mRNA in the paraventricular nuclei of deceased subjects. TRH levels were low in those with chronic versus acute illness. Low TRH levels correlated with low T3 and TSH levels. This is in contrast to rat models of hypothyroidism with low T3 levels, where the TRH was elevated. Other studies have shown the possible benefit of TRH infusion in the treatment of NTIS. [34 129 130 134] Finally, the alteration of the hypothalamus – pituitary axis as a major factor in NTIS is further

supported by the fact that the other central axes are also affected in critical illness, such as the suppression of the gonadotropins.

Cytokines, such as interleukin-1 (IL-1), IL-6, and tumour necrosis factor (TNF) are elevated in NTIS in correlation to severity of illness and have therefore been implicated in its pathogenesis. One could argue, however, that NTIS occurs in severe illness and cytokines are merely a marker of severe illness. Cytokine levels, especially IL-6, and cytokine receptor protein levels have been shown to be negatively correlated to T3 and T4 levels in adults with NTIS [14 15 31 56] These findings have been replicated in children undergoing cardiac surgery, and in children with acute respiratory infections. [48 79] Bacterial endotoxin administered to mice induced elevated cytokine production, decreased 5'- deiodinase mRNA, and decreased T3, T4, FT4, and FT3 levels. [13] IL-6 or TNF infusions can result in biochemical alterations of thyroid hormones similar to those found in NTIS. [124 137] However, attempts at neutralizing endogenous IL-6 have not been too successful in preventing these NTIS hormone changes. [16] A complete explanation as to a mechanism of the cytokines' role in NTIS is unclear. However, a study by Yu and Koenig using rat hepatocyte cultures illustrated that IL-1 and IL-6, but not TNF-alpha, decrease the T3 induction of D1. [147] The authors theorize that the increasing levels of cytokines successfully compete for gene transcription co-activators and therefore limit the supply for the deiodinase gene.

Leptin, a protein secreted by adipocytes, has also been studied as a possible factor in the pathogenesis of NTIS. Leptin levels are decreased during starvation and fasting, two clinical states classically associated with NTIS. Exogenous leptin provided during fasting can prevent the usual hormone changes seen in NTIS. [2 63] Legradi and colleagues illustrated that leptin administration normalized the previously suppressed proTRH mRNA in the hypothalamic paraventricular nucleus. [63] However, the leptin levels in surgery patients appear to differ from those seen in fasting and starvation. One study of pediatric cardiac surgery patients showed a decrease in leptin levels intraoperatively, an increase to above normal levels postoperatively, and then a return to normal levels about 24 hours after surgery. [83] A similar triphasic leptin response has been shown in adult surgery patients. [23]

Decreased levels of thyroid binding proteins and inhibition of binding and transport of T4 and T3 have been suggested as a possible factor in the low thyroid hormone levels in NTIS. Increased levels of free fatty acids and bilirubin have been implicated in this. [24 44 65]

The role of the elevated RT3 itself has also been studied. Infusions of pharmacological doses of RT3 in rats decreased the levels of T3 and impaired conversion of T4 to T3. [28] However, a study in which RT3 was given orally to humans resulted in no changes in T4, T3, or TSH levels. [117] RT3 is generally considered to have no significant biological effects however some have suggested

that it may have a role in the detrimental clinical and physiological activity in NTIS. [116]

Several clinical factors have been implicated as triggers of the thyroid hormone changes in NTIS. As described in the previous sections, intraoperative factors cited as triggers for NTIS in CPB patients include hemodilution by the CPB prime solution [73 81], thyroid binding inhibitory effects of heparin [44], hypothermia [105], and pulsatile versus nonpulsatile flow [87]. However, one would expect that any effect of these intraoperative factors should be short lived and therefore not necessarily explain any prolonged changes. The type of cardiac lesion may also be a factor in the degree of NTIS. [74] One study specifically attempts to identify distinct clinical factors that put children at most risk of developing NTIS following cardiac surgery. [102] Plumpton and Haas studied 36 infants less than 12 months of age following cardiac surgery for a variety of congenital heart lesions. Thyroid biochemistry was measured up to POD 2. Increased CPB time, decreased weight, and age less than 3 months were associated with decreased FT3 levels immediately after surgery. Increased cross-clamp time and intraoperative hypothermia resulted in lower TSH levels on POD 1, while interestingly, and in contrast to other studies, dopamine use resulted in higher TSH levels. These associations did not continue on POD 2. Prolonged ventilation beyond 48 hours was associated with lower FT3 and TSH levels on POD 2. Arguably this study does not identify risk factors but rather associations as it is a relatively short term

study and the sequential timing of the appearance of the various parameters in relation to the thyroid biochemistry changes can not be elucidated.

Medications can alter thyroid metabolism. As mentioned, dopamine is classically implicated in exacerbating NTIS with the suppression of TSH, T4 and T3. [55 132] This suppression resolves within hours of stopping the dopamine. RT3 is not elevated by dopamine as it is in classic NTIS. Glucocorticoids can also transiently affect thyroid metabolism through suppression of TSH. Brabant and colleagues describe the suppression of TSH levels and TSH pulses but a normal response to TRH stimulation following dexamethasone administration. [17] The authors conclude that this implies a supra-pituitary site of the glucocorticoid action. Iodine exposure through topical iodinated antiseptics has also been implicated in exacerbating NTIS. [47] However, studies have shown that the effect of this iodine exposure appears to be minimal. [21 67] In addition, if there is an effect, it tends to be a rise in the TSH level in response to a state of hypothyroidism which is contrary and easily differentiated from the TSH response seen with NTIS. [106]

A recent study indicates that in an optimal ICU setting nutrition does not affect thyroid hormone levels. No relation was found between thyroid hormone changes and the adequacy of protein and energy intake in 84 critically ill neonates and children followed for 6 days. [51] Since selenium is important for deiodinase enzyme function it has also been identified as a possible factor in NTIS. [50 61] The serum concentration of selenium decreases following CPB surgery. [50] A Cochrane

review on selenium supplementation in critically ill adults concluded that there was no evidence for any benefit although the reviewed studies were described as limited in regards to their availability of outcome measures, sample size, and quality. [6]

2.4 Treatment of NTIS

Treatments of essentially all the various neuroendocrine changes in critical illness have been attempted in dozens of studies. While the concept of treating or supplementing critically ill patients with hormones may appear to be a risk free proposal, the GH studies provide a cautionary note. Early studies of GH supplementation in critical illness showed perceived benefit with decreased catabolism and improved nitrogen balance. [139] [141] Some studies also showed clinical improvement including a study in children with burns that showed improved healing time and decreased hospital time in those that received growth hormone. [49] However, a later large randomized placebo controlled multinational study showed increased mortality in critically ill adults receiving growth hormone. [125] Treatment in NTIS, perhaps the neuroendocrine change for which treatment has been most frequently studied, is discussed in detail in the following section.

2.4.1 Treatment of NTIS in Adults

Treatment of NTIS with T4 or T3 has been attempted in various clinical scenarios although most commonly in adults undergoing CPB surgery. Generally, T4

therapy has not been successful. This should be expected given the suspected underlying endogenous defect in the conversion of T4 to the metabolically active T3 in patients with NTIS. T3 therapy has resulted in arguably mixed results.

Some animal studies in CPB have shown improved survival and inotropic effects with T3 supplementation [58 91 92] A basic science model with pig myocytes illustrated that pre-treatment with T3 improves myocyte velocity of shortening after hypothermic arrest and rewarming. [142] This may be suggestive that pre-treatment of human patients may improve left ventricular function.

Much of what is described in the human studies is dependent on the outcome measures and how their importance is interpreted. In a small study, Novitzky and colleagues randomized adults undergoing coronary artery bypass to intraoperative and postoperative T3 therapy or placebo. [89] The treatment group showed increased FT3 levels as expected. In those patients with preoperative ejection fractions less than 30%, the treatment group showed decreased inotropic and diuretic requirements compared to the placebo group. There was no difference in any of the hemodynamic measures or mortality between the treatment and placebo group. In those patients with preoperative ejection fractions greater than 40%, there was no difference in the required inotropic or diuretic requirements between the two groups. However, in this subset the treatment group did have increased stroke volume and cardiac output, and decreased vascular resistance. In a non randomized study, these same authors have also described beneficial

outcomes using T3 as a rescue therapy in postoperative cardiac surgery patients who either had difficulty weaning from CPB support or had ongoing poor myocardial function. [90] A larger randomized study with 170 CPB surgery patients found similar results with improved ventricular function, lower inotropic requirements, less need for mechanical device intervention, and decreased ischemia in the group treated with intraoperative and postoperative T3 compared to placebo. No difference was found in vascular resistance in contrast to the previous study. Differences in mortality did not reach statistical significance. [85] Others have found less positive results or have chosen to interpret the results differently. Similar to the other studies, Klemperer and colleagues found that CPB surgery patients treated with T3 had improved cardiac output and stroke volume and decreased vascular resistance in a randomized study of 142 patients. [57] However, they stress that the more important clinical outcomes such as the time to wean from CPB, inotrope requirements, duration of mechanical ventilation, length of ICU stay, length of hospital stay, incidence of major postoperative complications, and mortality did not differ between the treatment and placebo group. Therefore they conclude that T3 therapy is not warranted despite its positive inotropic effects.

There have also been some therapy studies in adults with NTIS and not cardiovascular disease. Brent and Hershman randomized 23 critically ill men with very low T4 levels to either intravenous T4 therapy for 14 days or placebo. Not surprisingly, the treated group had normal TT4 and FT4 levels earlier, on day 3

compared to day 13 in the control group. However, the T3 levels did not differ between the two groups. Despite no difference in the absolute T3 value on any given day, the control group did have an earlier significant improvement in the T3 and FT3 levels compared to the treated group. In addition, the treated group had a greater elevation of RT3 levels and suppression of the TSH levels compared to the control group. This likely indicates that the exogenous T4 was not able to be converted to T3 and in fact was being metabolized to RT3. The inability of patients with NTIS to convert exogenous T4 to T3 has been shown in other studies. [66] Overall there was a high mortality in this study with 17 of the 23 patients dying. A low T4 level was an inclusion criteria for the study, so the high mortality rate merely confirms previous studies that illustrated that a low T4 level was predictive of mortality. [119] The deaths were distributed evenly between the treatment and control groups but there was an increased mortality from days 5 to 17 in the treated group, which did not reach statistical significance. The baseline T3 level and the T3/T4 ratio were significantly higher in the survivors of both groups. In another randomized study, T3 therapy did not affect mortality or the resting metabolic rates in a cohort of burn patients. [8]

Some recent studies have focussed on therapy with releasing factors, such as TRH, as opposed to peripheral hormones, such as T3. It is thought that this approach may be more physiological by respecting the usual feedback loops and therefore allowing for easier less exact dosing. Studies with TRH, GH releasing peptide-2, and gonadotropin - releasing factor (GnRH) have shown some promise.

Infusions of these releasing factors lead to increased secretion and pulsatility of TSH, GH, and LH, and increased levels of T4, T3, insulin growth factors - I, insulin growth factor - binding protein 3, and testosterone. [129 130 134] Generally, the administration of a combination of the releasing factors leads to better results than when they are used alone. [129] Clinical outcome studies in this area are still lacking.

2.4.2 Treatment of NTIS in Children

Despite the arguable lack of clear clinical evidence that NTIS is harmful in children, and therefore requiring intervention, there have been some attempts with small studies to investigate the possible benefits of perioperative thyroid supplementation in children with congenital heart disease undergoing cardiac surgery and CPB. The impetus underlying the desire to carry out these studies includes the documented low levels of measured thyroid hormones in these patients, some previous evidence in animal models and in adults with cardiac disease that may demonstrate positive physiological effects of T3 on cardiac function including increased contractility and decreased vascular resistance, and the previous adult treatment studies that show some debatable clinical benefits. The NTIS changes, specifically the decreases in T3 and TSH, may be greater in children than adults and therefore the possible physiological effects may also be greater. [77] As with many treatment studies, the difficulties in the analysis and comparison of these studies include their heterogeneous choice of outcome measures, treatment protocols, and patient populations. In addition, since

perioperative mortality is fortunately rare in this pediatric population the relevance of the clinical benefits outlined in many of these studies seems open to discussion.

Chowdhury and colleagues conducted a prospective study randomizing children to treatment with continuous T3 infusion to maintain T3 levels within the normal range or no treatment. [26] Children, aged 0 to 18 years old, were assessed and included in the study if their serum TT3 on POD 0, 1, or 2 was below 40 ng/dl (0.6 nmol/L), or 60 ng/dl (0.9 nmol/L) in the neonates. Included patients were also required to be on mechanical ventilation. Twenty-eight eligible children were randomized with 14 in each group. NTIS was evident in all patients with a nadir in TT3 at 24 to 48 hours. Not surprisingly, the TT3 levels rose in the treatment group within 24 hours of initiation of the T3 infusions. There was no difference between the two groups in the assessed outcome measures of illness severity measured by TISS score, inotrope score, mechanical ventilation days, or hospital days. A subanalysis of a small cohort of the 9 neonates, with 5 in the treatment group, did show significant improvements in the TISS and inotrope scores in the treatment group. The mixed venous oxygen saturations, mechanical ventilation days, and hospital stay days trended towards improvement in the treatment group but none of these differences reached statistical difference. There was no difference in adverse events including changes in blood pressure, heart rate or dysrythmia between the two groups. This study is reportedly ongoing under the direction of one of the original authors. [37]

An infant population was also specifically studied by Portman and colleagues in a randomized prospective study of 14 children less than 1 year of age undergoing surgical repair of perimembranous ventricular septal defects, some of whom had underlying tetralogy of Fallot. [104] The seven patients in the treatment group received intravenous T3 before initiation of CPB and intraoperatively after the release of the aortic cross clamp. Inotrope requirements, including the use of dopamine, were equivalent in both groups. Serum FT3 and TT3 levels increased in the treatment group in the first 24 hours but then decreased and were equivalent to the control group at 72 hours, the end of the observation period. TT4 levels declined equally in both groups. The heart rate was transiently higher at 1 and 6 hours after surgery in the treatment group. Systolic and diastolic blood pressures were not different between the two groups. One patient in the treatment group had an episode of supraventricular tachycardia and it appears from the published graphs that some patients had heart rates greater than 160 beats per minute within a few hours after surgery. [37] There were no other adverse events reported. The serum half-life for exogenous T3 was determined to be 16 hours which is higher than in older children and adults. Other clinical outcomes, such as ventilation and hospital days, were not assessed in this study. This group is currently involved with a Food and Drug Administration (FDA) funded trial looking at perioperative thyroid hormone supplementation in children less than 2 years of age with an enrolment goal of 200 patients. [37 103] The Portman and Chowdhury studies were the only two included studies in a Cochrane review assessing perioperative

thyroid supplementation in infants undergoing cardiac surgery. [37] The review concluded that there is not sufficient evidence from randomized trials as to the harm or benefit of thyroid supplementation in this population. The review highlights the lack of standard measured outcomes and dosing methods.

In 2005, following the publication of the Cochrane review, Mackie and colleagues published a randomized controlled study looking at 72 hour postoperative continuous T3 infusion treatment in 42 neonates undergoing either a Norwood procedure or a two ventricle repair of an interrupted aortic arch and VSD soon after birth. [46 69] As expected, the T3 and FT3 levels were higher in the treatment group at 24, 48 and 72 hours postoperatively. At the next scheduled measurement, 7 days postoperatively, the levels were equal between the two groups. Other thyroid hormone measures including TT4, FT4, TSH, and T3U did not differ between the two groups. Cardiac index values, inotrope scores, ICU days, hospital days, heart rate, and diastolic blood pressure did not differ between the two groups. The clinical outcome score was 2.0 (range 0-4) in the treatment group and 2.0 (range 0-7) in the placebo group. The difference in the outcome scores' ranges did result in a statistically significant difference between the two groups ($p = 0.046$). The clinical outcome score was a composite of three variables including days to negative fluid balance, sternal closure, and extubation with a possible range of total score of 0 to 7. When assessed individually, the only variable found to differ between the two groups was days to negative fluid balance. The treatment group achieved negative fluid balance a half day quicker than the

control group, a difference of questionable clinical significance. The treatment group also had higher systolic and mean blood pressures. Two adverse events requiring discontinuation from the study were reported in the treatment group. One patient was hypertensive and the other developed ectopic atrial tachycardia. Of note, the tachycardia also recurred days after discontinuation of the T3. One patient in the placebo group, who was withdrawn from the study because extracorpeal membrane oxygenation support was required intraoperatively, died.

The only other randomized study of NTIS treatment in children studied 40 children, aged 2 days to 10 years, undergoing various types of cardiac surgeries, and therefore not as homogeneous a population as in the previously described studies. [10] In addition, all patients in this study received dopamine. Therefore, comparison to other studies may be somewhat blurred. Patients were randomized to either a daily T3 bolus or placebo for up to a maximum of 12 days postoperatively, with a median treatment period of 5 days. The treatment group reached above normal levels of T3 soon after receiving the first dose of T3. Yet, both groups had normal T3 levels by the time of discharge from hospital. The treatment group had better cardiac index scores, systolic function, and treatment scores. The cardiac function improvement was most evident in patients who had longer operation and CPB times. A close look at the study shows that other important clinical indicators including ICU, hospital, and ventilation days did not differ statistically between the two groups.

There have been other nonrandomized studies and reports that have looked at NTIS treatment in children undergoing cardiac surgery. [12 22 27 75 109] Mainwaring administered one bolus of T3 intraoperatively followed by one bolus postoperatively to 10 children, aged 19 to 42 months, undergoing modified Fontan procedures. [75] These children were then compared to 8 historical controls. FT3 and TT3 levels were higher in the treated patients at 1 hour, 5 days, and 8 days postoperatively, but interestingly not at 24 hours. The FT4 and TT4 levels were also higher in the treated patients. The treated group had statistically shorter ventilation hours and hospital days compared to the historical controls. Prior to his group's randomized study described above, Chowdhury published a report describing improved cardiorespiratory status in an index case of a child undergoing a Fontan procedure, along with 5 additional cases. [27] Carrel also described improved cardiorespiratory function in 5 children undergoing cardiac surgery for congenital heart defects who received T3 infusions during their postoperative courses. [22] In an abstract publication, Rosen described improved hemodynamics in 4 children receiving T3 following surgeries for complex congenital heart diseases. [109] In a short communication, Bialkowski also conveys success using T3 supplementation in children following cardiac surgery, but he also describes a complication of persistent hypotension in one such patient. [12]

The Mainwaring group also carried out a pharmacokinetic study in another cohort of 28 children undergoing modified Fontan procedures. [71] Patients received either placebo or one of three increasing intravenous doses of T3. The measured TT3

and FT3 levels were found to be dose dependent and the half life of T3 was calculated as 7 hours. This is about one third shorter than in adults and about half of that described previously in the randomized trial by Portman and colleagues. [103]

Thyroid supplementation has also been attempted in the neonatal population. Cochrane Collaboration reviews have shown no benefit of prophylactic thyroid hormone therapy in preterm infants with low thyroid hormone levels in regards to improving neonatal mortality, morbidity, respiratory distress syndrome or neurodevelopment. [93-96]

In conclusion, the published treatment studies do arguably show some improvement in selected outcomes, mostly physiological cardiac function, in children undergoing cardiac surgery and receiving T3 supplementation. The adverse events described to date appear to be minimal although the number of patients studied is still relatively small. However, the results of truly important measures of clinical outcome still seem to be unclear. Perhaps, the ongoing larger trials will better be able to clarify this. It could also be argued that the underlying basic question of whether NTIS is harmful is still not clear. While the biochemical thyroid hormone changes of NTIS unquestionably occur in critically ill children, especially those undergoing cardiac surgery, one must still ponder whether NTIS is the cause or merely a marker of critical illness? T3, both endogenous and exogenous, does have what appears to be a positive inotropic physiological effect

on cardiac function. But does supplemental T3 truly translate to improved clinical outcomes? Even more importantly, do NTIS and its resulting decrease in T3 serve as an important adaptive response in critical illness that should not be altered?

2.5 Is NTIS Adaptive or Maladaptive?

Are the changes in NTIS adaptive or maladaptive? All the studies on the neuroendocrine changes in critical illness, and NTIS in particular, are essentially trying to answer this same question. NTIS may be an adaptive response to decrease the catabolic effects of critical illness. Conversely, NTIS may be maladaptive with the decreased thyroid hormone levels leading to physiological and clinical deterioration. As evident in the above literature review, there are studies that support both these theories. Studies have shown that nonsurvivors of critical illness may in fact show less NTIS changes [53] and that treatment may delay normal biochemical recovery [20]. The other evidence in support of NTIS being adaptive, or perhaps more correctly "not maladaptive", is that many of the treatment studies do not show relevant clinical improvement. However, there are studies outlined in the preceding chapter that show possible physiological, biochemical, and arguably clinical improvement with treatment, lending support to the possible maladaptive effects of NTIS. Several studies do show an association of NTIS with severity of illness or mortality. However, these studies do not necessarily prove a causal relationship. It is not clear whether NTIS causes illness or whether illness causes NTIS. Only a couple of the studies in children undergoing cardiac surgery have attempted to assess this further by comparing

NTIS to illness severity. [3 11] Based on the limited data, the conflicting results amongst studies, and the still small patient numbers the question of the adaptive or maladaptive role of NTIS in children is still unclear. As outlined previously in this chapter, my study should add valuable information to the literature to assist in better answering that question.

CHAPTER 3: HYPOTHESES AND OBJECTIVES

3.0 Neuroendocrine Changes in Critically Ill Children Study

This study investigated nonthyroidal illness syndrome (NTIS) in a population of children who underwent cardiac bypass surgery.

3.1 Hypotheses

This study was undertaken to show the natural course of the acute neuroendocrine changes involving the hypothalamic-pituitary-thyroid axis that occur in children undergoing cardiac bypass surgery. This population of children was selected as a homogeneous representation of critical illness in children. It was expected that all the patients would show a degree NTIS. The degree of NTIS was expected to correlate will illness severity and overall clinical status. It was anticipated that the large majority of patients would spontaneously recover within a short period of time but that a subset of patients with an increased severity of illness and prolonged recovery period may be identified. If unique parameters of thyroid function are present in this subset of patients, they could be used to identify or predict such patients in a clinical setting and/or to identify a subset of patients where future trial of intervention may be warranted.

3.2 Objectives

The first objective of the study was to determine the natural course of changes to the hypothalamic-pituitary-thyroid axis in children who have undergone cardiac

bypass surgery. The second objective was to correlate these changes in the hypothalamic-pituitary-thyroid axis with short term outcome, clinical status, and illness severity.

CHAPTER 4: METHODS

4.0 Location

The study was performed at the Stollery Children's Hospital in Edmonton, Alberta, Canada. The study was reviewed and approved by the Health Research Ethics Board of the University of Alberta and the local health authority, Capital Health.

4.1 Study Population

Thyroid function was measured in 21 patients, aged 1 to 11 years, undergoing elective cardiac bypass surgery for repair of congenital heart lesions. Patients were not eligible for the study if they were less than one year of age, weighed less than 10 kilograms, had a preexisting endocrine disease including thyroid, adrenal or pituitary dysfunction, or had a condition predisposed to thyroid dysfunction (e.g. Trisomy 21). Patients undergoing an atrial septal defect repair, simple valve repair, or simple valve replacement were also not approached for enrollment in the study as their predicted recovery time was significantly shorter compared to the other study patients. Eligible patients were identified through prearranged access to the surgical schedules of the 2 local pediatric cardiac surgeons. Patients were identified sequentially and approached preoperatively in the outpatient Pre-assessment Clinic (PAC) to obtain informed consent from their parents or guardians. Patients were enrolled from November 2003 to February 2005.

4.2 Outcome Measures

Biochemical thyroid function, measures of clinical status, and measures of illness severity were collected on each patient as outlined below.

4.2.1 Thyroid Function

Thyroid function was measured by plasma levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), total triiodothyronine (TT3), triiodothyronine uptake (T3U), free triiodothyronine index (FT3I), and reverse triiodothyronine (RT3). Blood samples were drawn preoperatively within 1 week of surgery, postoperatively upon arrival to the Pediatric Intensive Care Unit (PICU), and then twice daily at 0800 and 2400 hours up to and including postoperative day (POD) 3, and then at 0800 hours from POD 4 to 7 inclusive as long as the patient remained in the PICU. The day of surgery was labeled as POD 0. Upon transfer to the ward from the PICU, the thyroid function was measured daily until POD 7 or discharge from hospital, whichever came first. Daily thyroid function measurement was also discontinued if the routine daily blood draws for clinical care was discontinued by the patient's healthcare team (n = 3).

4.2.1.1 Laboratory Assays

Samples were batched and stored at -70° Celsius until assayed. Samples were assayed in the hospital's clinical trials laboratory by immunoassays routinely used at the time in both the local clinical and clinical trials laboratories. The assays were done in two batches. TSH, FT4, and T3U were measured by ADVIA

Centaur assays with direct chemiluminometric technology (Bayer Corporation). The TSH assay was a two site sandwich immunoassay (normal range 0.40 to 6.00 mU/L for 1 to 5 year olds and 0.30 to 5.00 mU/L for 5 to 14 year olds, sensitivity and range 0.01-150 mU/L, intraassay coefficient of variation (CV) 2.48%, interassay CV 5.31%). The FT4 assay was a competitive immunoassay (normal range 8-20 pmol/L, sensitivity and range 1.3-155 pmol/L, intraassay CV 2.31%, interassay CV 1.95%). The T3U assay was a double antibody competitive immunoassay (normal range 0.22-0.37, sensitivity and range 0.1-1.0, intraassay CV 2.58%, interassay CV 1.42%). TT3 was measured by the Elecsys 2010 competitive assay with direct chemiluminometric technology (Roche Diagnostics, normal range 0.9-2.8 nmol/L, sensitivity > 0.3 nmol/L, intraassay CV 3.0%, interassay CV 8.0%). FT3I was calculated by the laboratory with the equation (TT3 x T3U) / 0.30 (normal range 0.9-2.8). RT3 was measured by the Biodata Reverse T3 competitive radioimmunoassay (Biodata Diagnostics, normal range 90-350 ng/L, sensitivity and range 25-2000 ng/L, intraassay CV 8.54%, interassay CV 8.66%). Thyroid hormone values reported below the detectable lower limit of the assay (e.g. TT3 < 0.3 nmol/L) were recorded as the lower limit (e.g. TT3 = 0.3 nmol/L) for the purpose of this study.

4.2.2 Clinical Measurements

Clinical data was extracted by chart reviews by the principal investigator or a research assistant. Clinical status and illness severity were measured in all patients by Pediatric Logistic Organ Dysfunction (PELOD) scores (figure 1) [64] in the

PICU, inotrope scores (figure 2) in the PICU, dopamine use, preoperative weight, total days in the PICU, total days in hospital, and total days of ventilation. Operative data collected included cardiac bypass time duration, aortic cross clamp time duration, intraoperative steroid use, and minimum nasal or esophageal temperature.

4.3 Statistical Analysis

4.3.1 Sample Size

A sample size of 20 patients gives 95% confidence half-widths, or precision, of 0.5 based on a sample standard deviation (SD) of 1 for T3 levels. Actual estimates of T3 SD were difficult to extract, however, results from three studies [1 10 11] were approximately 0.5, 0.7, and <2. Allen (1989), Murzi (1995), and Betterndorf (1997) [3 11 87] estimate baseline T3 levels greater than 2 and Allen (1989), Bettendorf (2000) and Murzi (1995) [3 10 87] estimate day 1 T3 levels at 0.7, 0.8 and 1. With this sample size, power is greater than 98% to detect a difference of 1 unit between these 2 time points using a paired Student t-test with an assumed SD of 1 and a 0.05 significance level.

4.3.2 Data Analysis

Data analysis was performed using SPSS 15 (SPSS Inc., Chicago, Ill, USA. 2006) and SAS 9.1 (SAS Institute Inc., Cary, NC, USA. 2002-2003) software. Data was analyzed for statistical significance at the alpha level of 0.05. Summary statistics

(e.g. mean, SD) were used to describe continuous variables (e.g. age, TSH). Frequencies and proportions were used to describe categorical, or discrete, variables (e.g. gender, type of surgery). Graphs of the individual hormone levels and sample population mean estimates across time-points were generated to illustrate the natural course of changes to the thyroid function. Changes in hormone concentrations over time points were assessed with paired Student t–tests and nonparametric Wilcoxon signed ranks tests. Possible correlations of short-term outcomes, such as PICU days or dopamine use, with point mean hormone estimates were assessed by Pearson correlation testing. The relation of early hormone estimates to clinical outcomes, such as hospital days, was also assessed by risk estimates and Fisher's exact testing.

Mixed effects models with a random intercept were used to examine the relationship between PELOD and inotrope scores with each hormone in order to properly account for the repeated measures aspect of the data. For both the PELOD and inotrope scores, treated as separate response variables, models were developed using either the AM or PM hormone samples as the predictor variable and therefore requiring 24 models (6 hormones x 2 for AM/PM x 2 for PELOD/inotrope). Residual plots, influential statistics and goodness-of-fit statistics were used to assess model assumptions and determine the best fit model, while appropriate transformations and/or non-linear terms (e.g. logarithmic transformations, quadratic functions) were used as necessary.

Comparison of hormone nadirs and peaks, PELOD and inotrope scores, and PICU, hospital, and ventilation days between sub groups were assessed with independent samples t-tests.

Figure 1: PELOD Score

DAILY PELOD

Pediatric Logistic Organ Dysfunction Score (PELOD)

PELOD Score	0	1	10	20	Maximum Score
Respiratory System: • PaO_2 / FiO_2 ratio • $PaCO_2$ mmHG (kPa) • **Mechanical Ventilation**	> 70 (9.3) and ≤ 90 (11.7) and no ventilation	ventilation	≤ 70 (9.3) or > 90 (11.7)		10
Caridovascular System: Heart rate (rate/min) • < 12 yr • ≥ 12 yr **Systolic BP (mmHg)** • 1 month • 1 month - 1 yr • 1 yr - 12 yr • ≥ 12 yr	 ≤ 195 ≤ 150 and > 65 > 75 > 85 > 95		 > 195 > 150 or 35 - 65 35 - 75 45 - 85 55 - 95	 < 35 < 35 < 45 < 55	20
Neurological System: Glasgow Pupillary reaction	12 - 15 and both reactive	7 --11	4 --6 or both fixed	3	20
Hepatic System: • ALT SGOT (UI/L) • PT or INR	< 950 and > 60 or < 1.4	≥ 950 or ≤ 60 or ≥ 1.4			1
Renal System: Creat: umol/L (mg/dL) • < 7 days • (7days - 1 year) • (1 year - 12 year) • ≥ 12	 < 140 (< 1.50) < 55 (< 0.62) < 100 (< 1.13) < 140 (< 1.59)		 ≥ 140 (≥ 1.50) ≥ 55 (≥ 0.62) ≥ 100 (≥ 1.13) > 140 (> 1.59)		10
Hematological System: White blood cell (10^9/L) Platelet count (10^9/L)	> 4.5 and ≥ 35	1.5 - 4.4 or < 35	< 1.5		10
				TOTAL	71

Figure 2: Inotrope Score

INOTROPE SCORE

Type of Surgery:_____

Inotropes	Day 0 Date
Dopamine	Yes ☐ No ☐ ___mcg / kg / min Score:_____
Dobutamine	Yes ☐ No ☐ ___mcg / kg /min Score:_____
Epinephrine	Yes ☐ No ☐ ___mcg / kg / min Score:_____
Norepinephrine	Yes ☐ No ☐ ___mcg / kg / min Score:_____
Other	Yes ☐ No ☐ ___mcg / kg / min Score:_____
Total Score	

Dopamine:	1 point per mcg/kg/min	(e.g. 10 mcg/kg/min = 10 points)
Dobutamine:	1 point per mcg/kg/min	(e.g. 1 mcg/kg/min = 1 point)
Epinephrine:	1 point per 0.1 mcg/kg/min	(e.g. 0.5 mcg/kg/min = 5 points)
Norepinephrine:	1 point per 0.1 mcg/kg/min	(e.g. 0.5 mcg/kg/min = 5 points)

CHAPTER 5: RESULTS

5.0 Baseline Characteristics

Twenty-one patients (13 females) were enrolled in the study (table 1). Twenty-five patients and their parents were approached for consent to participate in the study, of which 4 declined. Patients were followed for a mean of 6.62 days after surgery (SD = 2.04, median = 8, range = 1 to 8). Eleven of the patients were followed for the maximum 8 days to POD 7. Another 4 patients were followed for 7 days to POD 6. One patient (patient 20) withdrew from the study on POD 1. The mean age of the patients was 57.71 months (SD = 36.19, median 45.00, range = 23.00 to 138.00), and the mean preoperative weight was 19.22 kg (SD = 13.23, median = 14.20, range = 10.80 to 68.80).

5.1 Surgical and Perioperative Characteristics

Types of surgeries performed included unifocalization, right ventricular – pulmonary artery (RV-PA) conduit, and ventricular septal defect (VSD) repair in 1 patient (patient 1), Fontan in 5 patients (patients 11, 12, 17, 18, and 19), Fontan re-operation in 4 patients (patients 2, 3, 4, and 5), VSD repair in 5 patients (patients 6, 7, 14, 15, and 20), aortic valvotomy (AV) with a planned but cancelled Ross procedure in 1 patient (patient 8), RV-PA conduit re-operation in 3 patients (patient 10, 16, and 21), right ventricular outflow tract obstruction (RVOTO) re-operation in 1 patient (patient 9), and 1 patient had an AV, RVOTO

and VSD repair (patient 13). Sixteen of the surgeries were performed by one surgeon and the remainder by one other. There were no perioperative deaths.

Mean cardiopulmonary bypass (CPB) time was 69.9 minutes (SD = 42.3, median = 54.0, range = 32.0 to 219.0) and mean aortic cross clamp time was 15.1 minutes (SD = 18.0, median = 10.0, range 0 to 67.0). The mean intraoperative minimum nasal or esophageal temperature was 33.12° Celsius (SD = 2.38, median = 33.70, range 24.90 to 36.10). Five patients received intraoperative corticosteroids. Nine patients received dopamine perioperatively. The mean postoperative PICU stay was 6.4 days (SD = 4.2, median = 5.0, range 2.0 to 16.0), and the mean hospital stay was 16.2 days (SD = 10.9, median = 12.0, range 5.0 to 40.0). Ventilation status was followed up to 8 days with the PELOD scores. The mean duration of mechanical ventilation was 4.0 days (SD = 2.7, median = 3.0, range 1.0 to 8.0).

Table 1: Baseline Characteristics

Age (mean months (SD), range)	57.71 (37.08), 23-138
Gender (nF (%))	13 (62)
Type of Surgery (n)	
• **Fontan**	5
• **Fontan Re-operation**	4
• **Unifocalization**	1
• **VSD**	5
• **Ross**	1
• **RVOTO**	2
• **RV-PA Conduit**	3
Total (n)	21

SD = standard deviation, n = sample size, F = female

5.2 Thyroid Hormone Concentrations

A total of 1279 thyroid hormone measurements were performed on the 21 patients including 207 TSH, 216 FT4, 214 TT3, 212 FT3I, 212 T3U, and 218 RT3 measurements.

Preoperative baseline thyroid function values were within the normal range for age in all patients. Patient 6 was found to have possible previously unrecognized hyperthyroxinemia. This patient's preoperative biochemistry was FT4 17.8 pmol/L, TT3 2.2 nmol/L, FT3I 2.6, T3U 0.36, RT3 315 ng/L, and TSH 2.12 mU/L. At the patient's first postoperative measurement, the FT4 rose to 64.4 pmol/L with TT3 1.8 nmol/L, FT3I 3.1, and TSH 3.45 mU/L, then came down to 24.8 pmol/L with TT3 1.4 nmol/L, FT3I 2.0, and TSH 0.48 mU/L at the POD 0 PM measurement. The FT4 rose to 82.7 pmol/L with TT3 1.4 nmol/L, FT3I 2.0, TSH 1.65 mU/L at the POD 3 AM measurement. The patient was discharged from hospital on the following day. The assays were batched and therefore these results were not known during the patient's perioperative period. The patient's physician was informed when these results were observed.

The summary statistics for each thyroid hormone are detailed in tables 2a to 2f. Individual patient results graphed over time are in figures 3a to 3f. The mean hormone values over time are graphed in figures 4a to 4f.

5.2.1 Thyroid Stimulating Hormone (TSH)

The TSH (table 2a, figures 3a and 4a) levels appeared to decrease on POD 0 in the PM, and remain low until POD 4. Using the paired Student t-test there was no evidence of a statistically significant decrease from preoperative levels until the AM of POD 1 ($p < 0.0001$). All the mean TSH levels from this time point until the PM of POD 3 differed from the preoperative levels (p range <0.0001 to 0.011). The lowest mean TSH level, measured in the PM of POD 2, was an 83% decrease from the preoperative levels. However, the mean TSH levels measured from the AM of POD 1 to the PM of POD 3 were not statistically different (p range = 0.095 to 0.429). The TSH levels appeared to start to rise on POD 4, at which time the levels were also statistically insignificant from the preoperative levels ($p = 0.743$). The levels then continued to rise and were 78% above preoperative levels by POD 7; but this rise above the preoperative levels did not reach statistical significance ($p = 0.070$).

5.2.2 Total Triiodothyronine (TT3)

The TT3 (table 2b, figures 3b and 4b) decreased to levels statistically below preoperative levels at the first postoperative measurement on POD 0 ($p < 0.0001$), and remained as such until the end of the study period (all $p < 0.0001$). The lowest mean TT3 level, measured in the PM of POD 2, was an 81% decrease from the preoperative levels. There was no evidence of a statistically significant difference between this level and the mean TT3 levels measured from the AM of POD 3 until POD 4 (p range = 0.075 to 0.831). The TT3 appeared to start to rise from these trough levels on POD 5 ($p = 0.012$ compared to POD 2 PM). The

mean TT3 levels were still 59% below and statistically different from the preoperative levels on POD 7 ($p < 0.0001$).

5.2.3 Free Triiodothyronine Index (FT3I)

The FT3I (table 2c, figures 3c and 4c) decreased to levels statistically below preoperative levels on POD 0 in the PM ($p < 0.0001$), and remained as such until the end of the study period (p range <0.0001 to 0.008). The lowest mean FT3I level was on POD 3 in the PM with a 74% decrease from preoperative levels. However, there was no evidence of a statistically significant difference between the mean FT3I levels measured from the PM of POD 1 until POD 5 (p range = 0.067 to 0.852). The FT3I appeared to start to rise on POD 4 but there was no evidence of a statistically significant difference until POD 6 and 7 ($p = 0.035$ and 0.003 compared to POD 3 PM). The mean FT3I levels were still 41% below and statistically different from the preoperative levels on POD 7 ($p = 0.008$).

5.2.4 Triiodothyronine Uptake (T3U)

T3U (table 2d, figures 3d and 4d) levels increased above preoperative levels throughout the postoperative period (p range < 0.0001 to 0.010). The increase was statistically significant at the first postoperative measurement on POD 0 ($p < 0.0001$). The mean T3U level on POD 6 was actually statistically insignificant compared to the preoperative levels ($p = 0.085$). This may have been due to the small sample size and large variability (SD) since on POD 4 the same value of 0.42 with a smaller SD was assessed as different from the preoperative levels.

This finding on POD 6 did not change when analyzed with nonparametric testing. There were 11 T3U samples assayed for POD 7, and 14 for POD 6. The highest mean T3U level was on POD 7 which was 55% above the preoperative levels ($p = 0.007$). However, there was no evidence of a statistically significant difference between the mean T3U levels measured from the AM of POD 0 onward (p range = 0.186 to 1.000).

5.2.5 Free Thyroxine (FT4)

The FT4 (table 2e, figures 3e and 4e) levels appeared to initially increase immediately postoperatively, but this change was not statistically significant ($p = 0.343$). FT4 levels decreased below the preoperative level by POD 1 in the AM ($p = 0.031$). Statistically, the FT4 levels were back to preoperative levels on POD 3 in the AM ($p = 0.747$) but this was likely influenced by the elevated levels in patient 6. Levels were then again statistically below the preoperative levels on POD 3 in the PM ($p = 0.001$) and on POD 4 ($p = 0.005$). FT4 levels returned to preoperative levels on POD 5 ($p = 0.995$). Analyzing the data without patient 6, the patient with hyperthyroxinemia, resulted in all the mean FT4 levels remaining significantly below the preoperative level until POD 4. The lowest mean FT4 level was on POD 3 in the PM with a 51% decrease from the preoperative levels. There was no evidence of a statistically significant difference between the mean FT4 levels measured in the PM of POD 1 ($p = 0.169$), and the levels from the PM of POD 2 until POD 6 (p range = 0.066 to 0.730). The FT4 levels appeared to

start to rise on POD 5, but there was no evidence of a statistically significant difference from the trough levels until POD 7 ($p = 0.002$).

5.2.6 Reverse Triiodothyronine (RT3)

RT3 (table 2f, figures 3f and 4f) started to rise above preoperative levels immediately postoperatively ($p = 0.015$), and then increased more so and remained above the preoperative levels until POD 6 (p range <0.0001 to 0.049). Levels were statistically back to preoperative levels on POD 7 ($p = 0.070$) but the mean on that day had large variability (SD). The highest mean RT3 level was on POD 2 in the PM with a 191% increase above the preoperative levels. There was no evidence of a statistically significant difference between the mean RT3 levels measured from the PM of POD 0 until the AM of POD 3 (p range = 0.181 to 0.756). The mean levels appeared to start decreasing on POD 4 but then increased again with the POD 6 and 7 levels showing no evidence of a statistically significant difference from the POD 2 PM levels ($p = 0.212$ and 0.435)

5.2.7 Nonparametric Testing

Nonparametric testing with the Wilcoxon Signed Ranks Test, instead of the paired Student t-test, to assess the differences from preoperative levels for all the hormones resulted in only minor differences. The statistical decrease of the TSH levels from the preoperative levels was earlier at POD 0 in the PM ($p = 0.008$) as opposed to POD 1 in the AM. The trough TSH levels from POD 1 in the PM until POD 3 in the PM again showed no evidence of statistical difference (p range =

0.066 to 0.916), but unlike with the paired Student t-test, the mean level in the AM of POD 1 did differ ($p = 0.031$). As with the paired Student t-test, the TSH levels were back to baseline on POD 4 ($p = 0.182$). Additionally, with the nonparametric testing the RT3 levels did not return to preoperative levels on POD 7 ($p = 0.010$). There was no difference in the nonparametric testing with or without patient 6. Analysis of the FT4 results with nonparametric testing was similar to those using the parametric paired Student t-test and not including patient 6.

Table 2a: Plasma Thyroid Stimulating Hormone Concentrations (mU/L)

	Mean (SD)	Median	Range	N
Preoperative	2.06 (0.81)	1.77	1.22-3.65	16
PICU Arrival	2.03 (1.20)	1.53	0.51-4.51	21
POD 0 PM	1.08 (1.80)	0.66	0.20-8.68	21
POD 1 AM	0.63 (0.76)	0.48	0.15-3.58	19
POD 1 PM	1.11 (1.45)	0.48	0.12-4.53	14
POD 2 AM	0.68 (0.68)	0.44	0.11-2.82	19
POD 2 PM	0.36 (0.28)	0.27	0.04-0.80	13
POD 3 AM	1.17 (1.51)	0.44	0.02-5.46	19
POD 3 PM	0.78 (0.78)	0.52	0.05-2.25	10
POD 4	2.04 (2.04)	1.33	0.04-7.95	16
POD 5	2.29 (1.71)	2.00	0.21-5.84	14
POD 6	2.58 (2.28)	2.26	0.21-8.95	14
POD 7	3.67 (2.51)	3.35	0.18-7.99	11

SD = standard deviation, N = sample size, PICU = pediatric intensive care unit, POD = postoperative day

AM samples were drawn at approximately 0800; PM samples were drawn at approximately 2400

Table 2b: Plasma Total Triiodothyronine Concentrations (nmol/L)

	Mean (SD)	Median	Range	N
Preoperative	2.44 (0.52)	2.30	1.50-3.30	17
PICU Arrival	1.59 (0.52)	1.40	0.80-2.90	21
POD 0 PM	0.98 (0.51)	0.90	0.30-1.90	21
POD 1 AM	0.79 (0.37)	0.85	0.30-1.70	20
POD 1 PM	0.66 (0.29)	0.70	0.30-1.30	15
POD 2 AM	0.63 (0.29)	0.60	0.30-1.20	19
POD 2 PM	0.46 (0.22)	0.40	0.30-1.10	14
POD 3 AM	0.65 (0.41)	0.50	0.30-1.60	19
POD 3 PM	0.47 (0.25)	0.30	0.30-0.90	11
POD 4	0.80 (0.59)	0.70	0.30-2.20	17
POD 5	0.88 (0.62)	1.00	0.30-2.10	15
POD 6	0.97 (0.67)	0.90	0.30-2.10	14
POD 7	1.01 (0.59)	0.70	0.30-1.90	11

SD = standard deviation, N = sample size, PICU = pediatric intensive care unit, POD = postoperative day,

AM samples were drawn at approximately 0800; PM samples were drawn approximately at 2400

Table 2c: Plasma Free Triiodothyronine Index

	Mean (SD)	Median	Range	N
Preoperative	2.50 (0.52)	2.55	1.60-3.40	16
PICU Arrival	2.26 (0.73)	2.10	1.00-4.00	21
POD 0 PM	1.37 (0.58)	1.40	0.40-2.40	21
POD 1 AM	1.14 (0.48)	1.20	0.40-2.20	20
POD 1 PM	0.95 (0.39)	1.00	0.40-1.70	15
POD 2 AM	0.87 (0.29)	0.90	0.40-1.40	19
POD 2 PM	0.66 (0.20)	0.60	0.50-1.20	14
POD 3 AM	0.86 (0.47)	0.70	0.10-2.00	19
POD 3 PM	0.65 (0.21)	0.60	0.50-1.10	11
POD 4	1.11 (0.68)	0.85	0.40-2.30	16
POD 5	1.18 (0.76)	1.00	0.40-2.50	15
POD 6	1.18 (0.66)	1.20	0.40-2.10	14
POD 7	1.47 (0.70)	1.40	0.60-2.70	11

SD = standard deviation, N = sample size, PICU = pediatric intensive care unit, POD = postoperative day,

AM samples were drawn at approximately 0800; PM samples were drawn approximately at 2400

Table 2d: Plasma Triiodothyronine Uptake Measurements

	Mean (SD)	Median	Range	N
Preoperative	0.31 (0.05)	0.30	0.24-0.46	16
PICU Arrival	0.43 (0.06)	0.43	0.32-0.52	21
POD 0 PM	0.44 (0.07)	0.44	0.33-0.52	21
POD 1 AM	0.45 (0.07)	0.47	0.31-0.54	20
POD 1 PM	0.43 (0.06)	0.42	0.30-0.52	15
POD 2 AM	0.44 (0.09)	0.44	0.30-0.58	19
POD 2 PM	0.45 (0.08)	0.48	0.32-0.57	14
POD 3 AM	0.43 (0.09)	0.42	0.27-0.64	19
POD 3 PM	0.45 (0.10)	0.49	0.31-0.58	11
POD 4	0.42 (0.09)	0.42	0.30-0.62	16
POD 5	0.44 (0.10)	0.42	0.30-0.66	15
POD 6	0.42 (0.12)	0.41	0.28-0.69	14
POD 7	0.48 (0.11)	0.46	0.27-0.70	11

SD = standard deviation, N = sample size, PICU = pediatric intensive care unit, POD = postoperative day, AM samples were drawn at approximately 0800; PM samples were drawn approximately at 2400

Table 2e: Plasma Free Thyroxine Concentrations (pmol/L)

	Mean (SD)	Median	Range	N
Preoperative	14.93 (4.06)	13.90	8.2-26.8	18
PICU Arrival	17.50 (11.14)	15.00	9.7-64.4	21
POD 0 PM	13.39 (4.55)	12.30	6.7-24.8	21
POD 1 AM	12.13 (5.00)	11.00	6.1-29.4	20
POD 1 PM	10.13 (3.21)	10.10	4.1-16.3	15
POD 2 AM	9.90 (2.53)	10.00	5.3-15.0	20
POD 2 PM	8.01 (2.71)	7.80	4.1-13.2	14
POD 3 AM	12.91 (17.16)	9.20	3.8-82.7	19
POD 3 PM	7.26 (2.97)	6.60	2.7-12.8	11
POD 4	9.36 (4.46)	8.30	3.1-17.4	17
POD 5	14.97 (12.20)	14.70	3.0-53.0	15
POD 6	12.42 (6.57)	11.65	3.3-23.1	14
POD 7	13.35 (4.85)	13.30	3.9-21.6	11

SD = standard deviation, N = sample size, PICU = pediatric intensive care unit, POD = postoperative day,

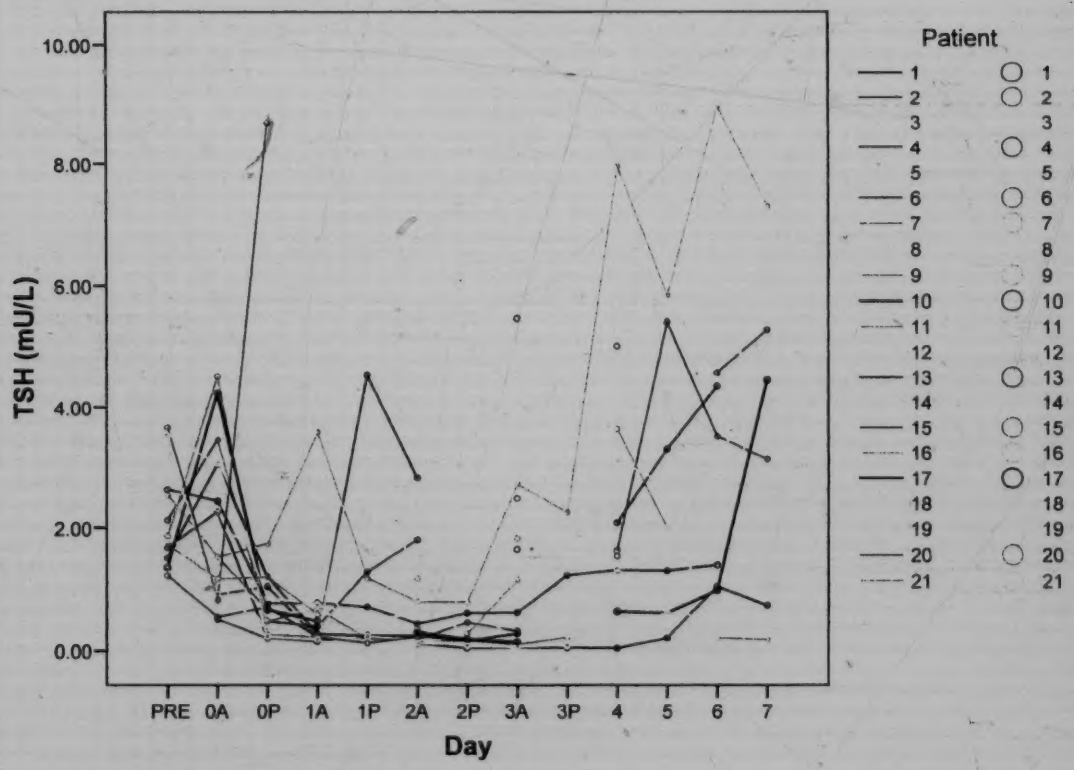
AM samples were drawn at approximately 0800; PM samples were drawn approximately at 2400

Table 2f: Plasma Reverse Triiodothyronine Concentrations (ng/L)

	Mean (SD)	Median	Range	N
Preoperative	322.95 (79.98)	312.5	143-448	20
PICU Arrival	406.62 (145.75)	382.0	163-808	21
POD 0 PM	809.81 (321.45)	830.0	287-1663	21
POD 1 AM	839.80 (230.06)	807.5	407-1166	20
POD 1 PM	934.73 (346.81)	947.0	386-1522	15
POD 2 AM	914.50 (355.84)	862.0	441-1643	20
POD 2 PM	940.07 (477.81)	778.0	389-1902	14
POD 3 AM	785.11 (373.34)	651.0	281-1752	19
POD 3 PM	788.91 (544.81)	653.0	247-1968	11
POD 4	650.88 (309.31)	561.0	237-1443	17
POD 5	722.73 (514.85)	559.0	268-2254	15
POD 6	753.50 (736.10)	560.0	232-3166	14
POD 7	849.09 (784.69)	552.0	242-3034	11

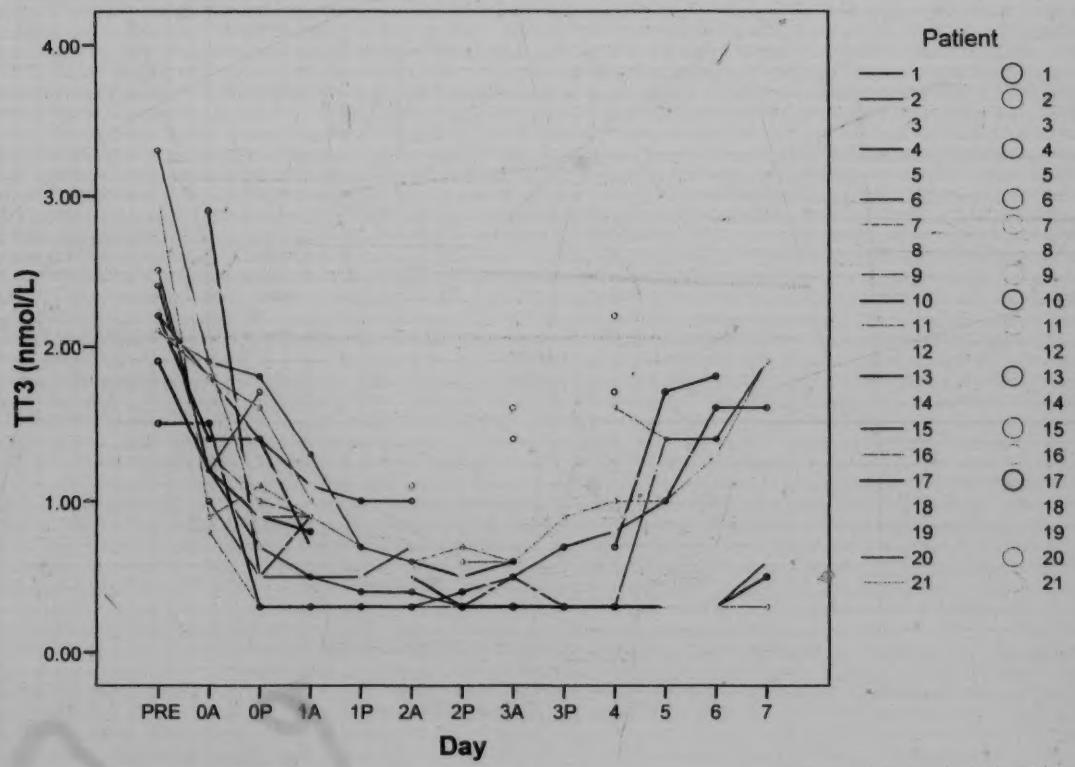
SD = standard deviation, N = sample size, PICU = pediatric intensive care unit, POD = postoperative day, AM samples were drawn at approximately 0800; PM samples were drawn approximately at 2400

Figure 3a: Plasma Thyroid Stimulating Hormone Concentrations in Individual Patients over the Duration of the Study



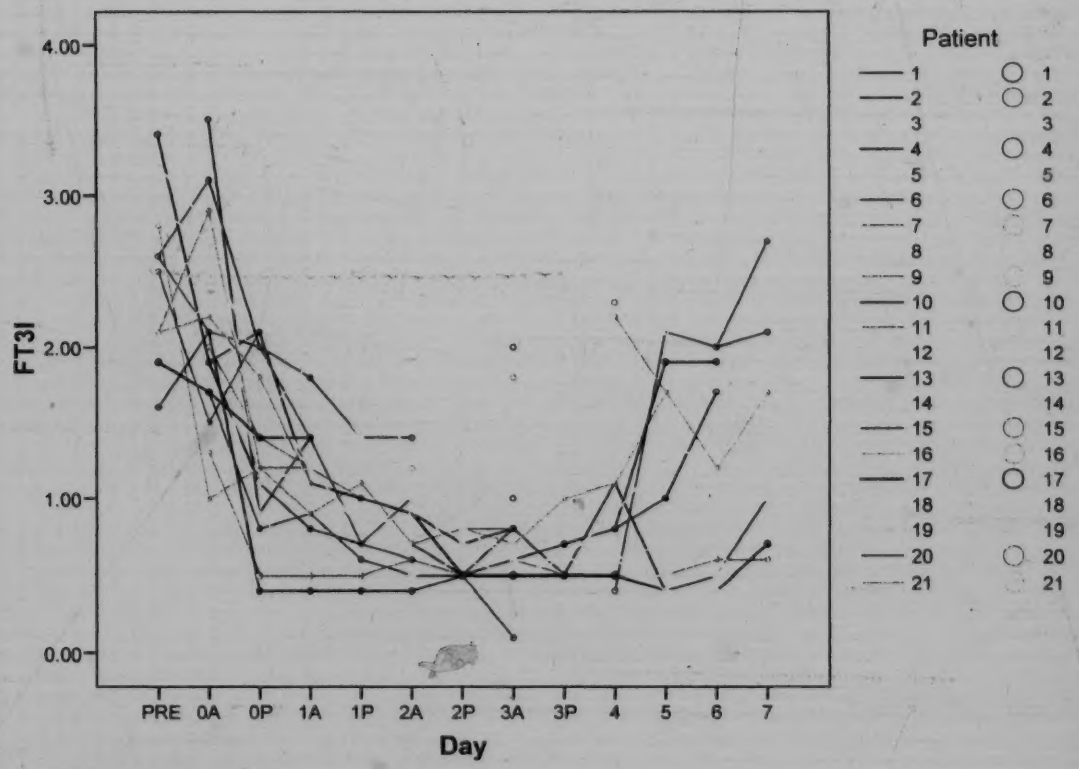
PRE = Preoperative, A= AM, P= PM

Figure 3b: Plasma Total Triiodothyronine Concentrations in Individual Patients over the Duration of the Study



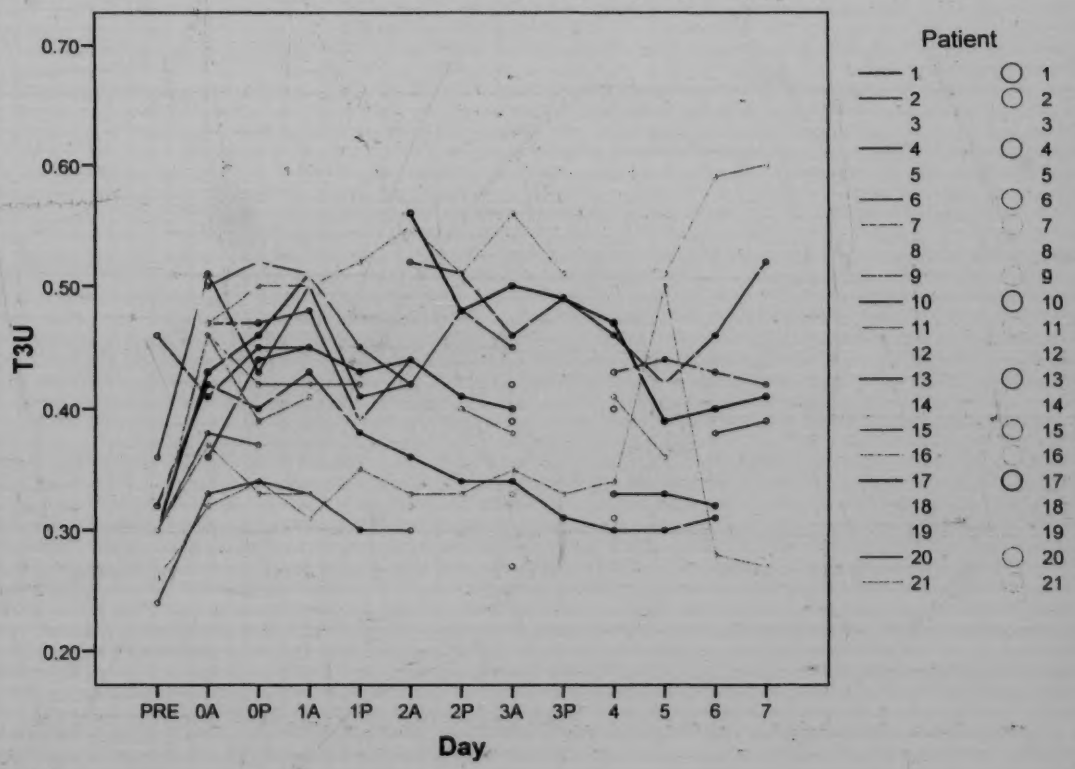
PRE = Preoperative, A= AM, P= PM

Figure 3c: Plasma Free Triiodothyronine Index in Individual Patients over the Duration of the Study



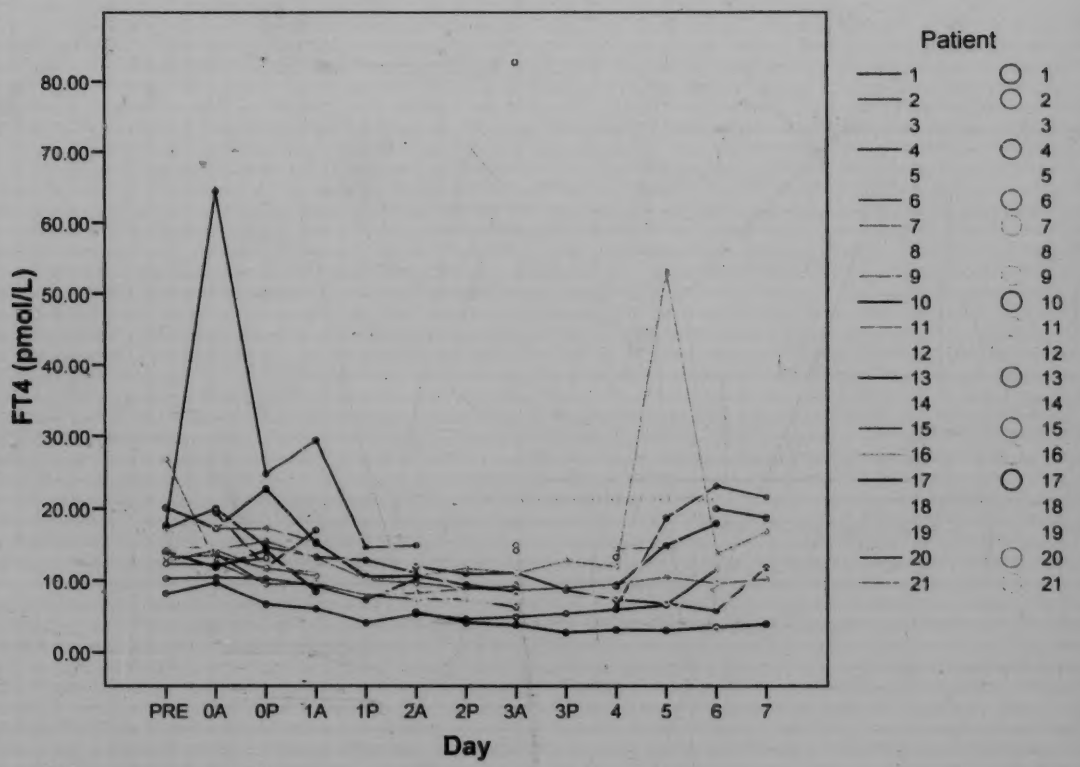
PRE = Preoperative, A= AM, P= PM

Figure 3d: Plasma Triiodothyronine Uptake Measurements in Individual Patients over the Duration of the Study



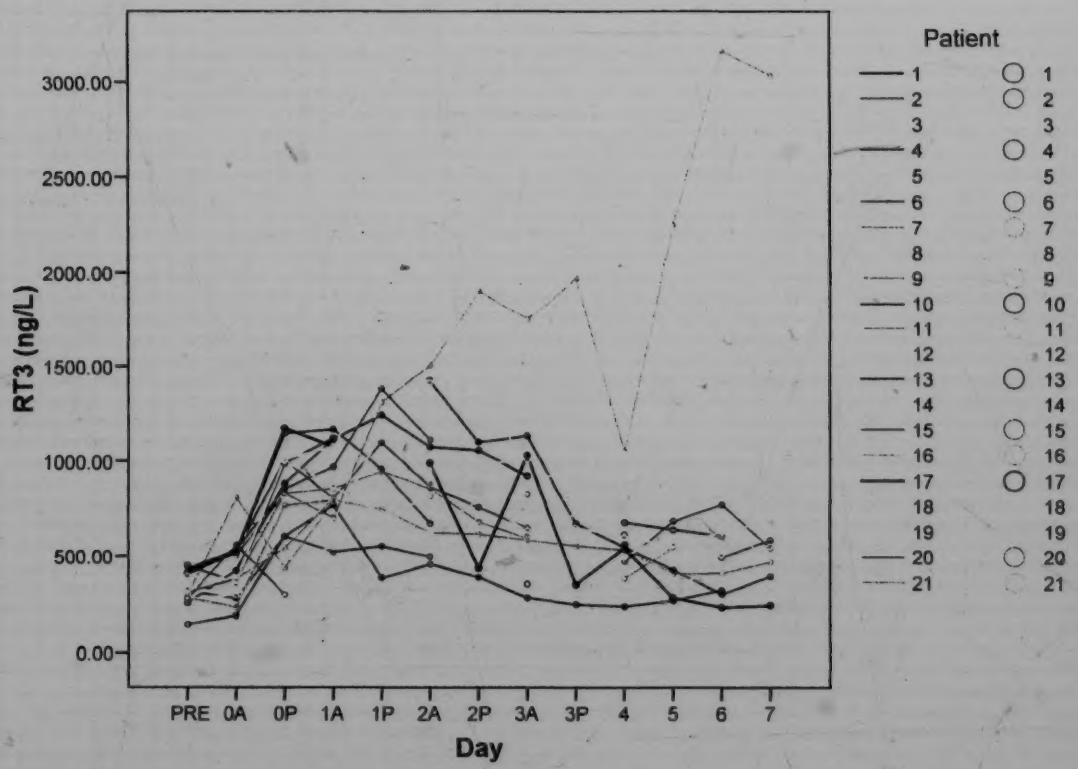
PRE = Preoperative, A= AM, P= PM

Figure 3e: Plasma Free Thyroxine Concentrations in Individual Patients over the Duration of the Study



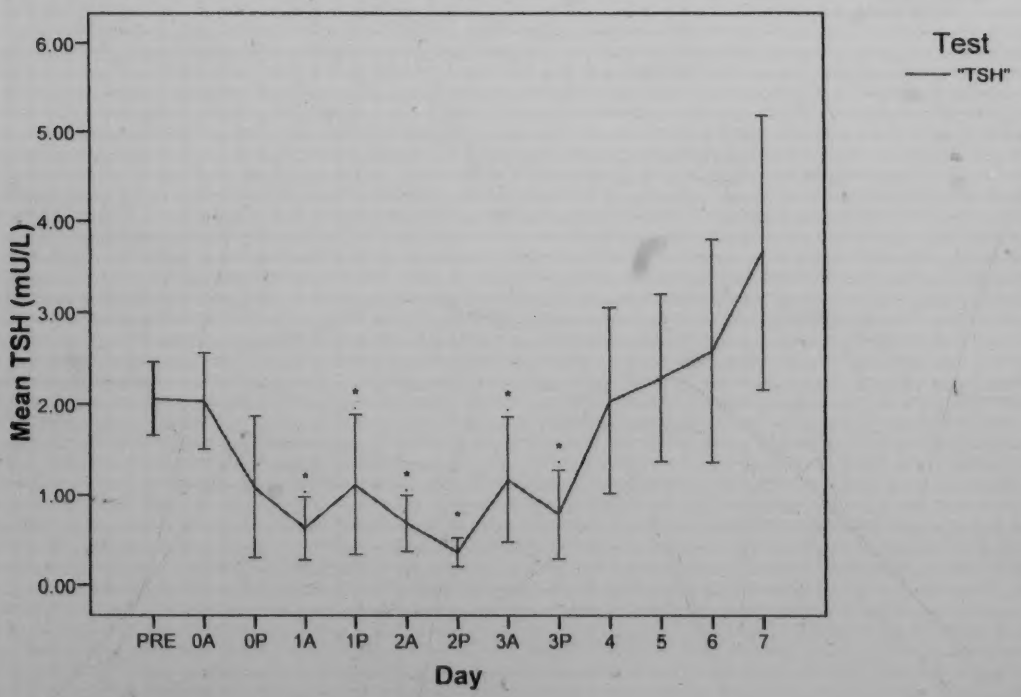
PRE = Preoperative, A= AM, P= PM

Figure 3f: Plasma Reverse Triiodothyronine Concentrations in Individual Patients over the Duration of the Study



PRE = Preoperative, A= AM, P= PM

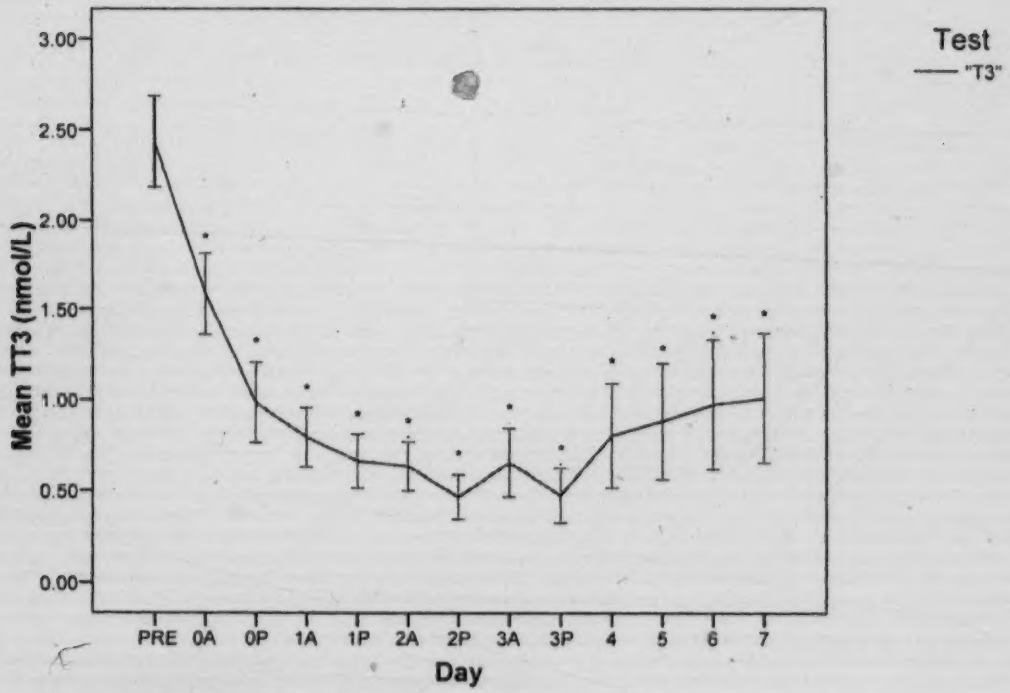
Figure 4a: Mean Plasma Thyroid Stimulating Hormone Concentrations



PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative value
Error bars: +/- 2 SE

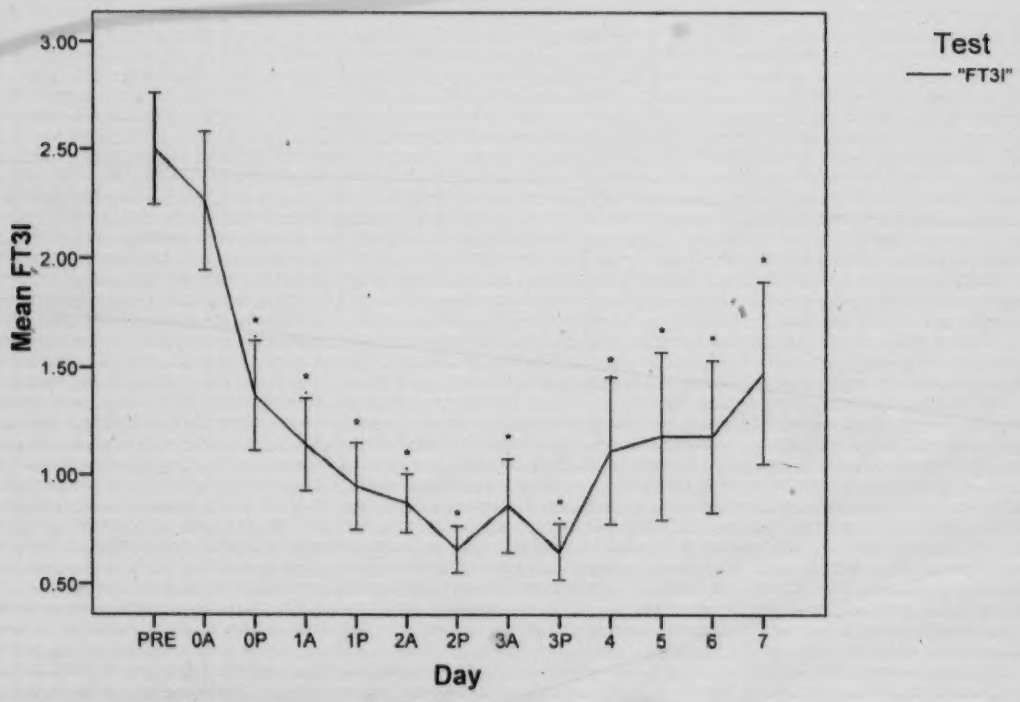
Figure 4b: Mean Plasma Total Triiodothyronine Concentrations



PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative value
Error bars: +/- 2 SE

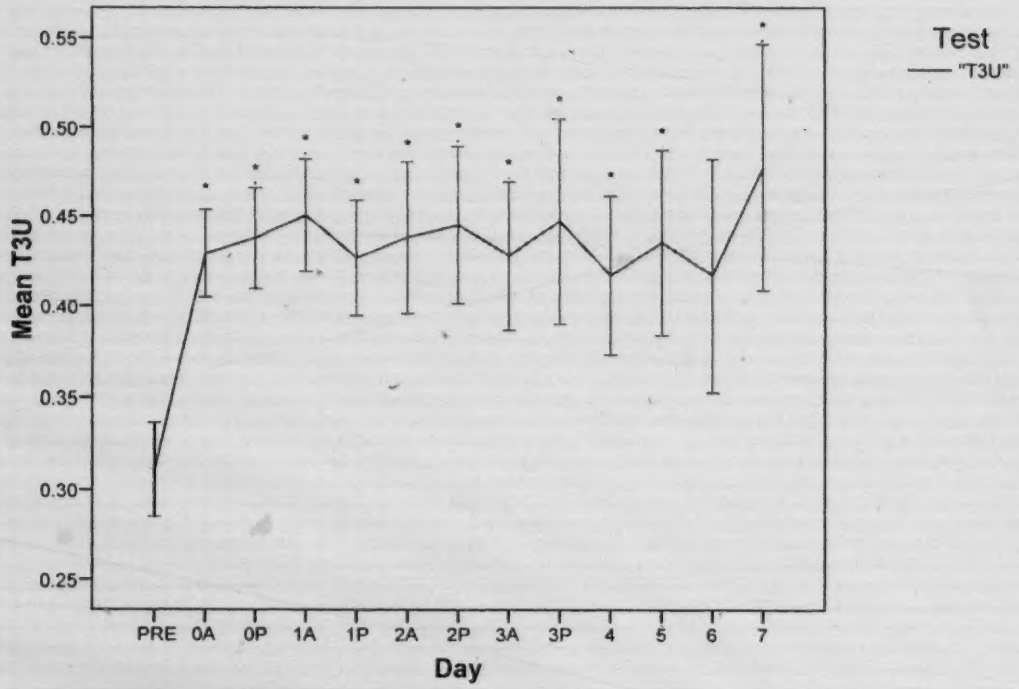
Figure 4c: Mean Plasma Free Triiodothyronine Index



PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative value
Error bars: +/- 2 SE

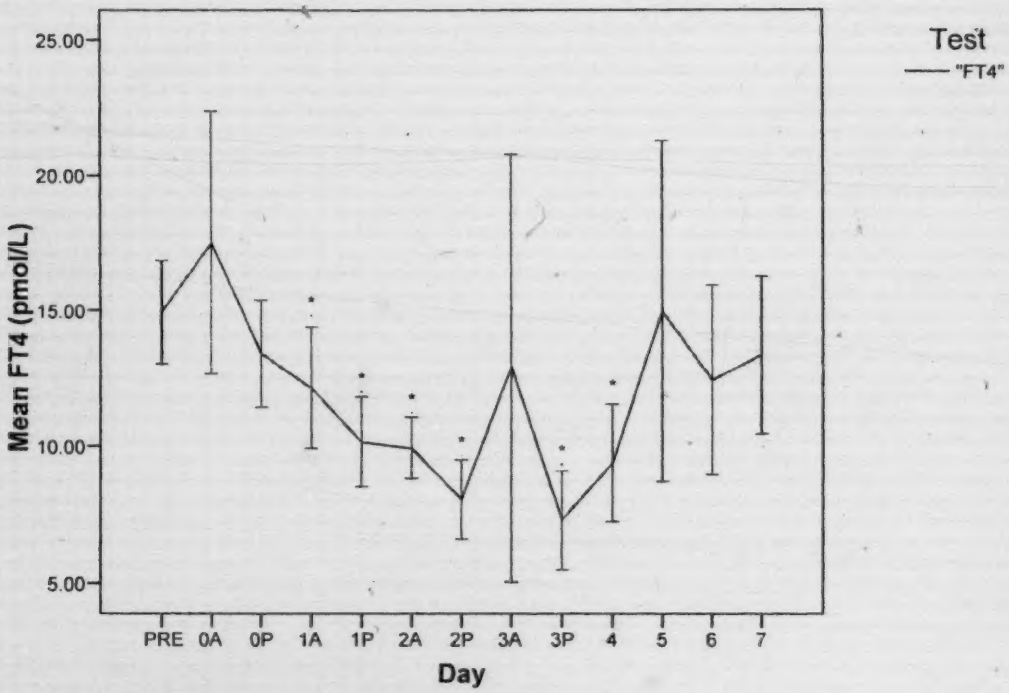
Figure 4d: Mean Plasma Triiodothyronine Uptake Measurements



PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative value
Error bars: +/- 2 SE

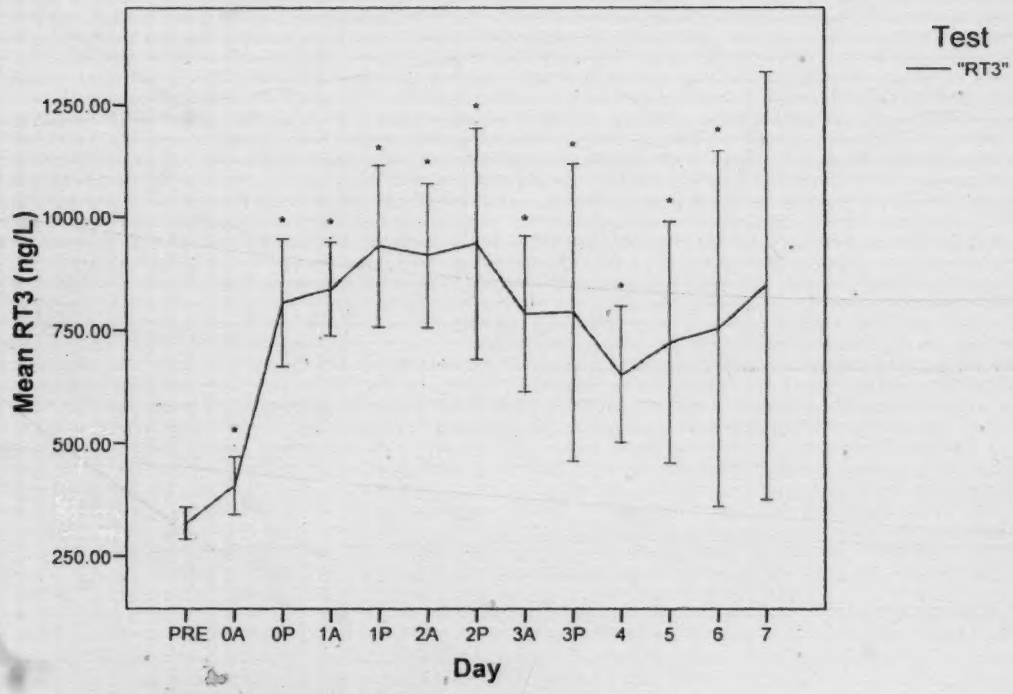
Figure 4e: Mean Plasma Free Thyroxine Concentrations



PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative value
Error bars: +/- 2 SE

Figure 4f: Mean Plasma Reverse Triiodothyronine Concentrations



PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative value
Error bars: +/- 2 SE

5.3 Correlation of Thyroid Hormone Levels to Clinical Characteristics and Status

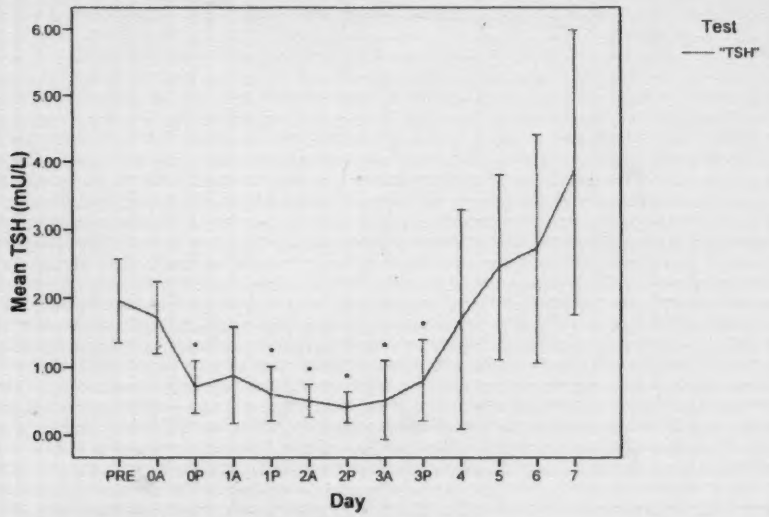
5.3.1 Dopamine Use

Separate analysis of the small group of 9 patients who received dopamine illustrated some differences in the natural history of their thyroid hormone changes compared to the group of 12 patients who did not receive dopamine.

There was no evidence that the highest or lowest mean levels differed between the two groups for any of the hormones measured (p range = 0.356 to 0.909). The initial decrease from preoperative levels was slightly earlier in the dopamine group with the TSH decreasing at POD 0 in the PM compared to POD 1 in the AM ($p = 0.013$). The FT4 decrease was also earlier at POD 1 in the AM ($p = 0.045$) compared to POD 1 in the PM. The initial increase in RT3 was delayed in the dopamine group to POD 0 in the PM ($p = 0.005$) compared to POD 0 immediately postoperatively. The RT3, TT3, T3U, and FT3I did not statistically return to preoperative levels by POD 7 ($p = 0.038, 0.001, 0.043, 0.004$). In contrast, in the non-dopamine group these 4 hormones returned to preoperative levels on POD 5, 6, 1 in the PM, and POD 3 in the PM, respectively ($p = 0.190, 0.157, 0.123, 0.136$). In addition, the dopamine group showed statistical evidence of a later return to preoperative levels with TSH at POD 4 ($p = 0.877$) compared to POD 3 in the AM, and FT4 at POD 5 ($p = 0.515$) compared to POD 3 in the AM.

The dopamine group had higher mean PELOD scores (p=0.027), PICU days (p= 0.014), and mechanical ventilation days (p=0.009) than the non-dopamine group. The mean PELOD score was 12.20 (SD = 5.75) compared to 6.92 (SD = 4.39). The mean stay in the PICU was 8.89 days (SD = 4.20) compared to 4.50 days (SD = 3.21), and the mean days of mechanical ventilation was 5.67 days (SD = 2.24) compared to 2.75 days (SD = 2.30). The mean inotrope scores and hospital days did not show evidence of any difference between the two groups.

Figure 5a: Mean Plasma Thyroid Stimulating Hormone Concentrations in Patients Treated with Dopamine

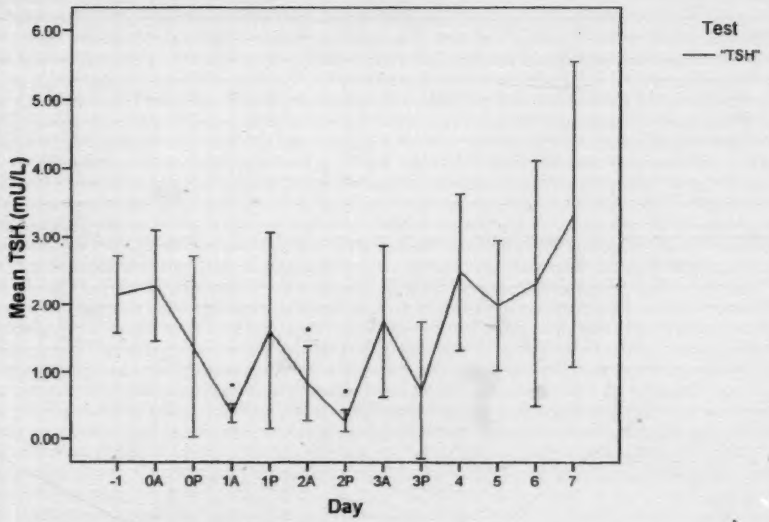


PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative values

Error bars: +/- 2 SE

Figure 5b: Mean Plasma Thyroid Stimulating Hormone Concentrations in Patients Not Treated with Dopamine



PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative values

Error bars: +/- 2 SE

5.3.2 Intraoperative Corticosteroid Use

The small size of the group of patients who received corticosteroids intraoperatively (n = 5) did not allow for analysis with paired Student T-tests to determine the timing of evidence of statistical hormone changes from the preoperative levels for this group. However, the patients who received corticosteroids were filtered out and analysis was performed separately on the group of 16 patients who did not receive corticosteroids intraoperatively. Comparing this subgroup of patients to the entire study population revealed only minor differences. The FT4 decrease from the preoperative levels was delayed and occurred on POD 1 in the PM ($p = 0.020$) instead of the AM ($p = 0.082$). The RT3 returned statistically to preoperative levels earlier on POD 6 ($p = 0.078$) instead of POD 7. Lastly, there was evidence that the TSH actually increased above the preoperative levels in the 4 patients remaining in the study on POD 7 with preoperative levels recorded ($p = 0.005$).

5.3.3 Fontan Procedures

The group of 9 patients who underwent either a Fontan or Fontan re-operation procedure was analyzed separately and compared to the group of 12 patients with non-Fontan procedures. The Fontan procedure is a complex one and previous studies of NTIS have found differing results in these patients compared to other pediatric cardiac surgery patients. [74] [75] The Fontan group was a large homogeneous proportion of the total population in this study and therefore afforded itself to be analyzed separately. This was a post-hoc analysis.

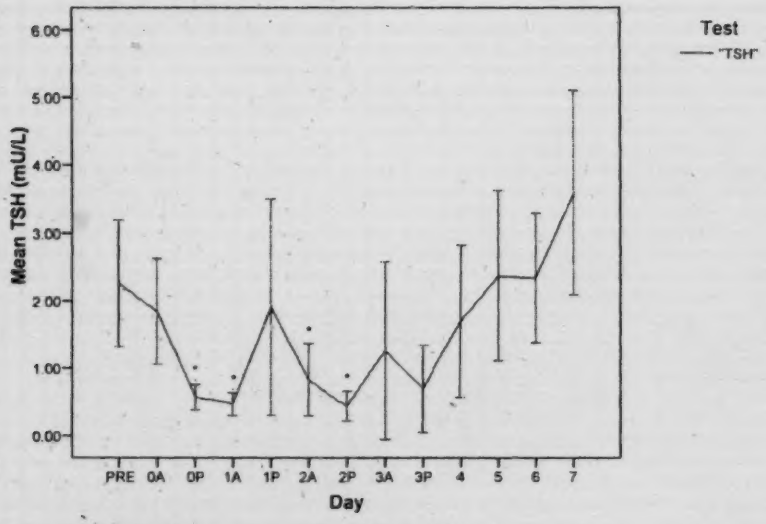
The natural histories of the mean hormone values for each group had similar patterns but exhibited some specific differences (figures 6a to 6l). The decrease in TT3 (figures 6c and 6d) was greater in the Fontan group. The mean TT3 on POD 3 in the PM was 0.32 nmol/L compared to lowest mean level of 0.59 nmol/L on POD 2 in the PM in the non-Fontan group ($p = 0.030$). In addition, the T3U (figures 6g and 6h) rose higher in the Fontan group to 0.52 on POD 3 in the PM compared to the highest mean level of 0.41 on POD 0 in the non Fontan group ($p = 0.001$). The other hormones did not show evidence of any differences in their lowest or highest mean levels.

The Fontan group showed an earlier statistical increase in the RT3 (figures 6k and 6l) levels from preoperative levels on POD 0 immediately postoperatively ($p = 0.004$) compared to POD 0 in the PM ($p < 0.0001$) in the non-Fontan group. The TT3 and T3U did not show evidence of a return to preoperative levels by POD 7 ($p < 0.0001$ and $p = 0.004$, respectively) in the Fontan group as compared to a return to preoperative levels on POD 6 ($p = 0.052$) and POD 2 in the PM ($p = 0.249$), respectively, in the non-Fontan group. The FT4 (figures 6i and 6j) levels decreased early in the Fontan group on POD 0 in the PM ($p = 0.048$) and remained statistically below the preoperative levels (p range = 0.001 to 0.027) until POD 5 ($p = 0.081$). The FT4 levels then decreased statistically from the preoperative levels again on POD 6 ($p = 0.027$) prior to returning to preoperative levels once again on POD 7 ($p = 0.097$). In contrast, in the non-Fontan group, the

FT4 levels did not differ from the preoperative levels in any convincing pattern. The only differences were at POD 2 in the AM ($p = 0.017$) and POD 3 in the PM ($p = 0.039$) but the sample size was small ($n = 4$) at this second time point. The TSH (figures 6a and 6b) levels decreased earlier at POD 0 in the PM ($p = 0.021$) in the Fontan group compared to POD 1 in the AM ($p = 0.004$) in the non-Fontan group. The TSH levels returned permanently to preoperative levels on POD 3 in the AM ($p = 0.115$) in the Fontan group. In the non-Fontan group the TSH also returned to preoperative levels on POD 3 in the AM ($p = 0.069$), but decreased again on POD 3 in the PM ($p = 0.012$), prior to returning to the preoperative levels permanently on POD 4 ($p = 0.640$). The pattern of the FT3I (figures 6e and 6f) levels did not statistically differ between the two groups.

The Fontan group had higher mean PELOD scores ($p = 0.012$), inotrope scores ($p = 0.005$), PICU days ($p = 0.019$), hospital days ($p = 0.005$), and mechanical ventilation days ($p = 0.009$) than the non-Fontan group. The mean PELOD score was 12.57 (SD = 3.58) compared to 6.65 (SD = 5.54), and the mean inotrope score was 12.97 (SD = 7.06) compared to 4.03 (SD = 5.74). The mean stay in the PICU was 8.78 days (SD = 4.49) compared to 4.58 days (SD = 3.03), the mean stay in hospital was 23.44 days (SD = 7.60) compared to 10.75 days (SD = 9.84), and the mean days of mechanical ventilation was 5.67 days (SD = 2.60) compared to 2.75 days (SD = 2.01).

Figure 6a: Mean Plasma Thyroid Stimulating Hormone Concentrations in the Fontan Patients

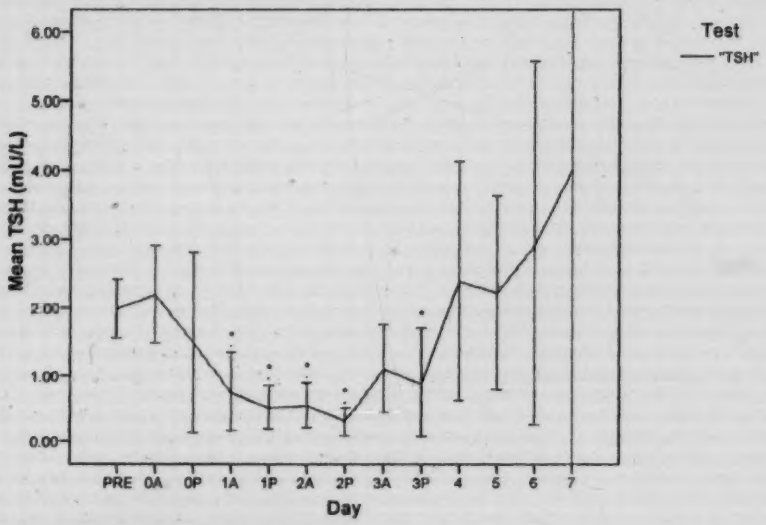


PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative values

Error bars: +/- 2 SE

Figure 6b: Mean Plasma Thyroid Stimulating Hormone Concentrations in the Non-Fontan Patients

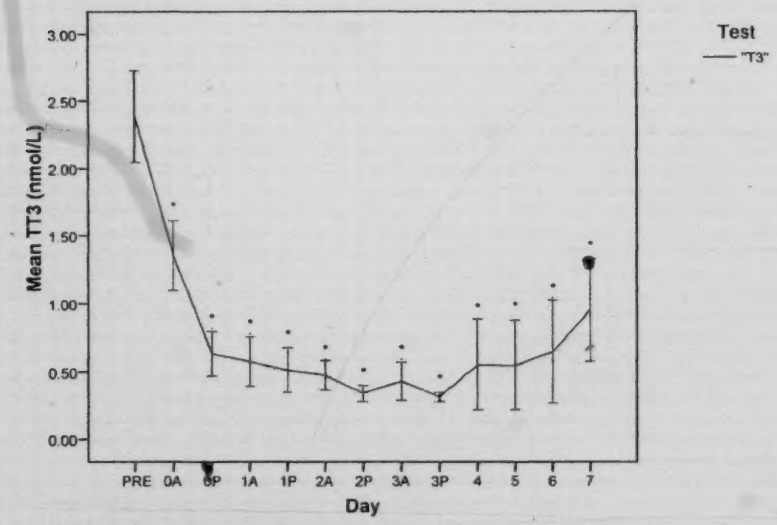


PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative values

Error bars: +/- 2 SE

Figure 6c: Mean Plasma Total Triiodothyronine Concentrations in the Fontan Patients

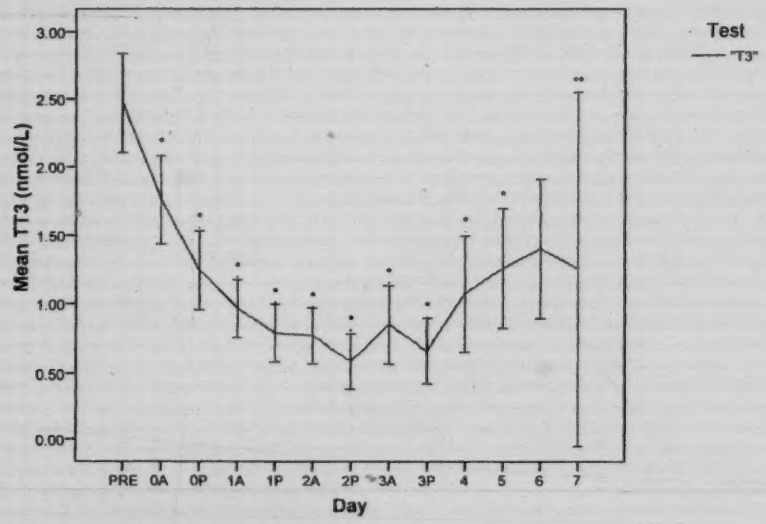


PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative values

Error bars: +/- 2 SE

Figure 6d: Mean Plasma Total Triiodothyronine Concentrations in the Non-Fontan Patients



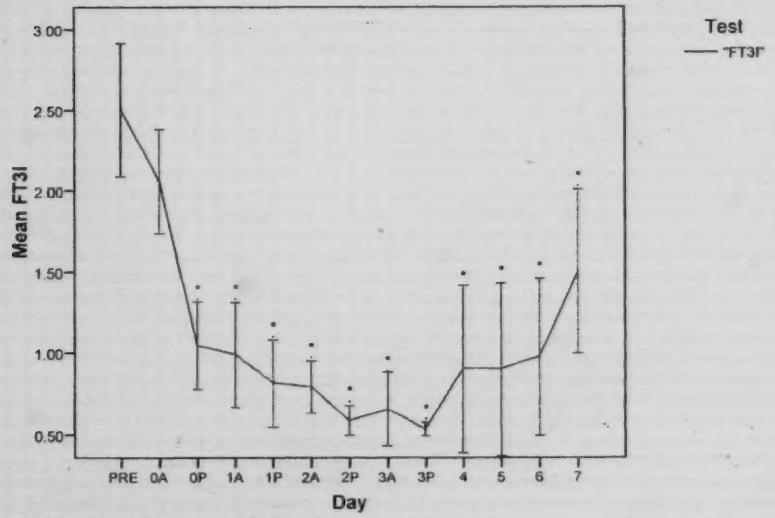
PRE = Preoperative, A = AM, P = PM

* = $p < 0.05$ compared to preoperative values

** = t cannot be computed because the sum of caseweights is less than or equal to 1

Error bars: +/- 2 SE

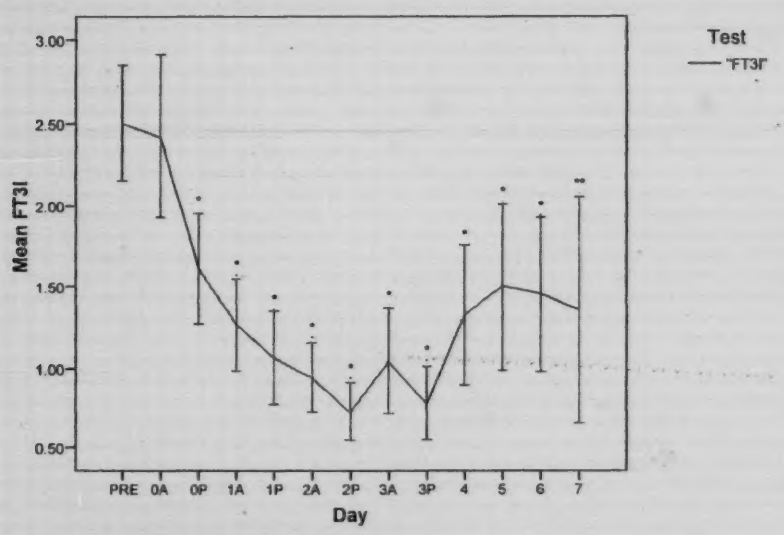
Figure 6e: Mean Plasma Free Triiodothyronine Index in the Fontan Patients



PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values
Error bars: +/- 2 SE

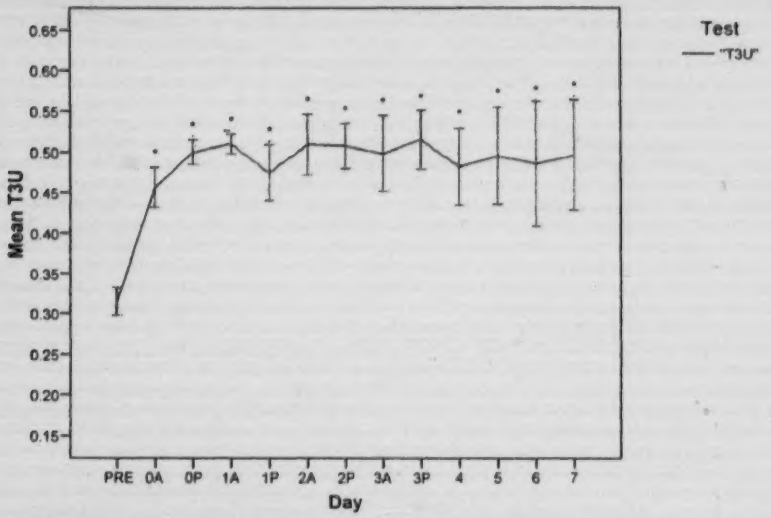
Figure 6f: Mean Plasma Free Triiodothyronine Index in the Non-Fontan Patients



PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values
** = t cannot be computed because the sum of caseweights is less than or equal to 1
Error bars: +/- 2 SE

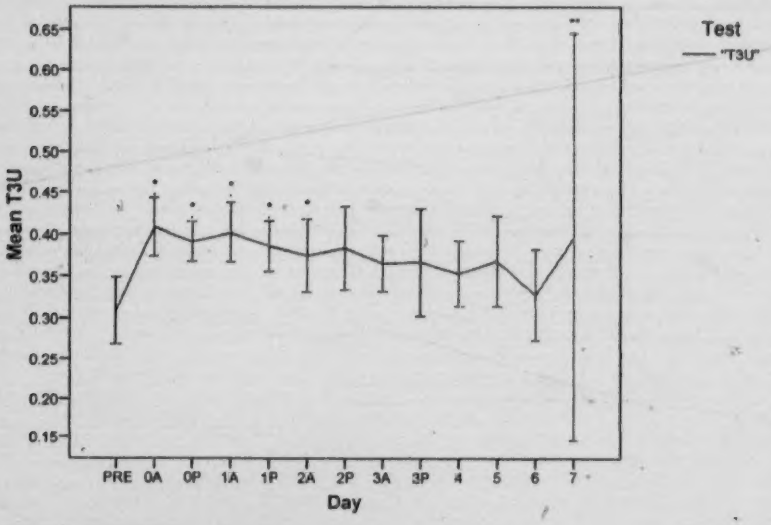
Figure 6g: Mean Plasma Triiodothyronine Uptake Measurements in the Fontan Patients



PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values
Error bars: +/- 2 SE

Figure 6h: Mean Plasma Triiodothyronine Uptake Measurements in the Non-Fontan Patients

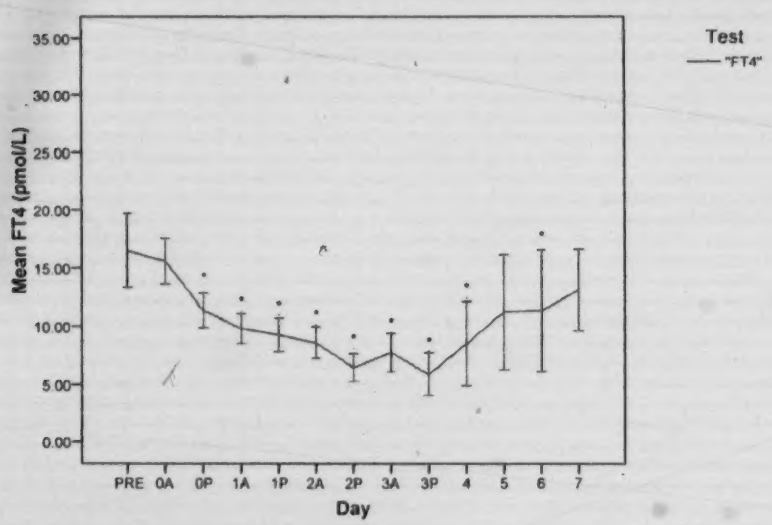


PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values
** = t cannot be computed because the sum of caseweights is less than or equal to 1

Error bars: +/- 2 SE

Figure 6i: Mean Plasma Free Thyroxine Concentrations in the Fontan Patients

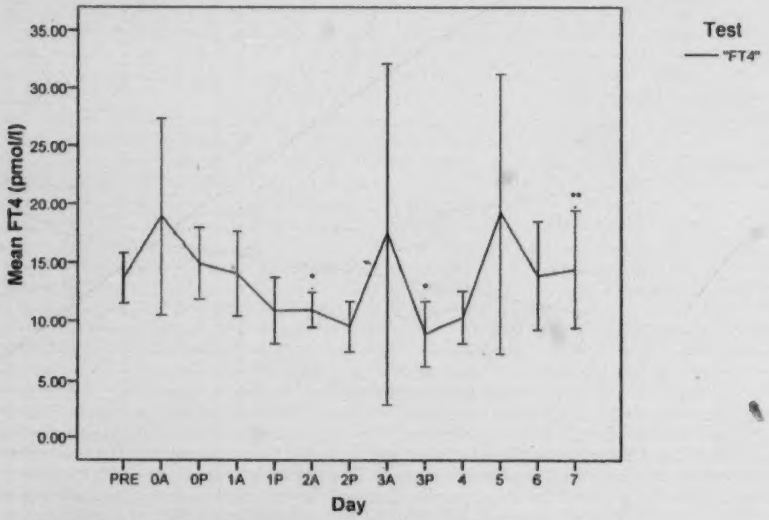


PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values

Error bars: +/- 2 SE

Figure 6j: Mean Plasma Free Thyroxine Concentrations in the Non-Fontan Patients



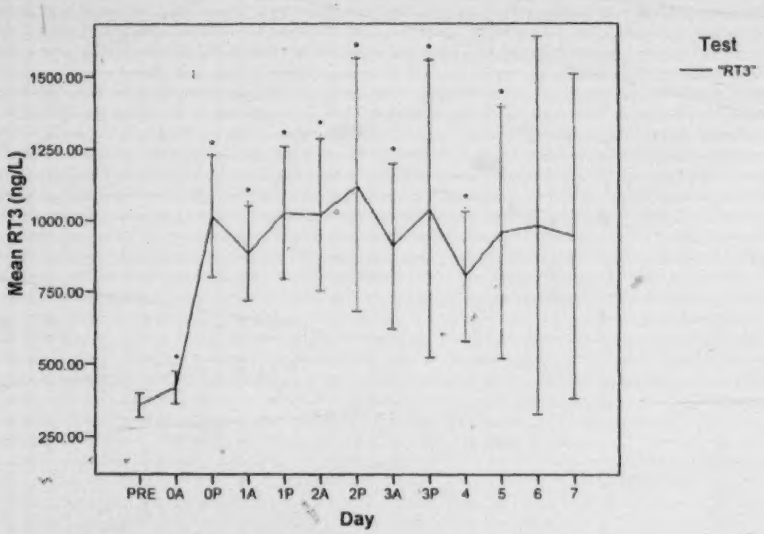
PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values

** = t cannot be computed because the sum of caseweights is less than or equal to 1

Error bars: +/- 2 SE

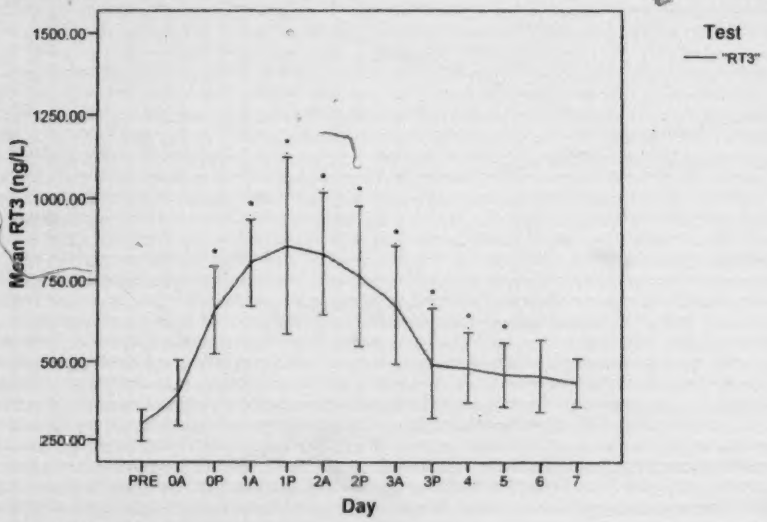
Figure 6k: Mean Plasma Reverse Triiodothyronine Concentrations in the Fontan Patients



PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values
Error bars: +/- 2 SE

Figure 6l: Mean Plasma Reverse Triiodothyronine Concentrations in the Non-Fontan Patients



PRE = Preoperative, A = AM, P = PM

* = p < 0.05 compared to preoperative values
Error bars: +/- 2 SE

5.3.4 Cardiopulmonary Bypass (CPB) and Aortic Clamp Time

CPB duration showed no evidence of correlation to the thyroid hormone levels. The aortic clamp time was correlated to the final RT3 levels on POD 7 ($r = 0.759$, $p = 0.007$).

5.3.5 Temperature

The minimal nasal or esophageal temperatures recorded during surgery were directly correlated to the FT3I ($r = 0.444$, $p = 0.044$) and TT3 ($r = 0.463$, $p = 0.035$) levels on POD 0, the day of surgery, in the PM. This implies that higher intraoperative temperatures lead to higher FT3I and TT3 levels at this specific time point. It should be noted that in general the recorded minimal temperatures (mean = 33.12 °C, SD = 2.38, median = 33.70, range 24.9 to 36.1) were not in the deep hypothermic range as is consistent with the expected care for the age of the patients included in the study. Therefore, a comparison of the effects of surgical temperature is difficult.

5.3.6 Weight and Age

The preoperative weight of the patients was correlated with the low FT3I levels on POD 3 in the PM ($r = 0.766$, $p = 0.006$) and the TT3 levels on POD 2 in the PM ($r = 0.774$, $p = 0.001$). The positive correlations imply that the heavier patients had less of a decrease in the FT3I and TT3 levels. Similar correlations were found with patient age and the FT3I and TT3 levels at these time points ($r = 0.813$, $p = 0.002$ and $r = 0.641$, $p = 0.014$, respectively). When the weight was

analyzed as Z-scores for age, there was no evidence of a correlation to the hormone levels ($r = -0.134$, $p = 0.695$ and $r = 0.013$, $p = 0.964$, respectively). This implies that age and not weight is the main correlation. Patient's age was also found to correlate with some markers of illness severity, more so than weight, including ventilation days ($r = -0.472$, $p = 0.031$), 4 of the 8 days of PELOD scores (r range = -0.872 to -0.470, p range = 0.001 to 0.049) and 5 of the 8 days of inotrope scores (r range = -0.934 to -0.445, p range = 0.002 to 0.043).

5.4 Correlation of Thyroid Hormone Levels to Illness Severity

5.4.1 PICU, Hospital, and Mechanical Ventilation Days

The thyroid hormone levels, at certain time points, were found to be correlated to the number of days spent in the PICU and hospital, and the number of days of required mechanical ventilation.

None of the thyroid hormone measurements done immediately postoperatively upon arrival to the PICU (POD 0 AM) were found to correlate to the PICU, hospital, or mechanical ventilation days. However, these three clinical outcomes were all positively correlated to the T3U levels ($r = 0.557, 0.655, 0.548$ and $p = 0.009, 0.001, 0.010$) on POD 0 in the PM, and inversely correlated to FT3I ($r = -0.620, -0.523, -0.525$ and $p = 0.003, 0.015, 0.015$) and TT3 ($r = -0.653, -0.642, -0.577$ and $p = 0.001, 0.002, 0.006$) levels also on POD 0 in the PM. All the patients who required at least 8 days of mechanical ventilation (n = 4) or 10 days

in the PICU (n = 5) had TT3 levels less than or equal to 0.7 nmol/L and T3U levels greater than or equal to 0.44 on POD 0 in the PM. A patient with a TT3 level of 0.7 nmol/L or lower on POD 0 in the PM had an odds ratio (OR) of 12.00 (95% confidence interval (CI) = 1.02 to 141.34) and a relative risk (RR) of 6.50 (95% CI = 0.88 to 48.34) of being in the PICU for 10 days or longer. Fisher's exact test revealed a p-value of 0.047 for this relation. Conversely, all the patients with TT3 levels greater than 0.7 nmol/L at this time point required less than 7 days of mechanical ventilation. All the patients requiring a hospital stay of 20 or more days (n = 8) also had T3U levels greater than or equal to 0.44, at this time point, with TT3 levels less than or equal to 0.9 nmol/L. All patients with T3U levels greater than or equal to 0.50 at POD 0 in the PM (n = 6) required hospital stays of 21 days or more. A patient with a T3U level of 0.50 or greater on POD 0 in the PM had an OR of 20.00 (95% CI = 1.66 to 241.72) and a RR of 4.17 (95% CI = 1.42 to 12.19) of being in the hospital for 20 days or longer. Fisher's exact test revealed a p-value of 0.014 for this relation. Hospital days were also inversely correlated to the FT4 levels ($r = -0.436$, $p = 0.048$), and positively correlated to the RT3 levels ($r = 0.512$, $p = 0.018$) at this time point.

The T3U levels were strongly correlated to PICU, hospital, and mechanical ventilation days. These levels correlated to the PICU days at all 11 time points from POD 0 in the PM up to an including POD 7 (r range = 0.897 to 0.511, p range < 0.0001 to 0.021), to the hospital days at 8 of these 11 measurements (r range = 0.725 to 0.563, p range < 0.0001 to 0.036), and to the mechanical

ventilation days at all except the last of these 11 measurements (r range = 0.926 to 0.507, p range < 0.0001 to 0.023).

The low FT3I in the PM of POD 3 was inversely correlated to PICU, hospital, and mechanical ventilation days (r = -0.603, -0.626, -0.628 and p = 0.049, 0.039, 0.039). In addition, PICU (r range = -0.786 to -0.475 p range = 0.001 to 0.049) and mechanical ventilation (r range = -0.871 to -0.517, p range < 0.0001 to 0.039) days were inversely correlated to FT3I at every time point from POD 3 to 7 inclusive and hospital days were inversely correlated to FT3I at 4 (r range = -0.715 to -0.479, p range 0.010 to 0.039) of these 6 measurements.

The low TT3 in the PM of POD 2 was inversely correlated to hospital days (r = -0.577, p = 0.031), but not PICU or mechanical ventilation days (r = -0.506, -0.503, p = 0.065, 0.067). However, all three of PICU, hospital, and mechanical ventilation days were inversely correlated to TT3 levels in 7 of the last 8 measurements done from POD 2 to 7 (r ranges = -0.824 to -0.617, -0.787 to -0.577, -0.907 to -0.585 and p ranges < 0.0001 to 0.008, 0.001 to 0.031, < 0.0001 to 0.008).

The FT4, TSH, and RT3 levels showed less consistent patterns of correlation with PICU, hospital, and mechanical ventilation days than those found with the T3U, FT3I, and TT3. The FT4 levels inversely correlated to PICU days on POD 4 and 6 (r = -0.606, -0.540, p = 0.010, 0.046), to hospital days on POD 6 (r = -0.690, p =

0.006) in addition to POD 0 in the PM as previously described, and to ventilation days on POD 4, 6, and 7 (r = -0.639, -0.657, -0.698 and p = 0.006, 0.011, 0.017). TSH inversely correlated to PICU and mechanical ventilation days on POD 3 in the AM (r = -0.503, -0.494, p = 0.028, 0.032). The high RT3 in the PM of POD 2 correlated to PICU days (r = 0.564, p = 0.036). RT3 also correlated with PICU (r = 0.517, 0.498, p = 0.020, 0.030) and mechanical ventilation (r = 0.486, 0.539, p = 0.030, 0.017) days at the AM measurements on POD 2 and 3. In addition, RT3 correlated with hospital days at those two AM measurements (r = 0.582, 0.545, p = 0.007, 0.016) and also at POD 4 (r = 0.514, p = 0.035).

5.4.2 PELOD Score

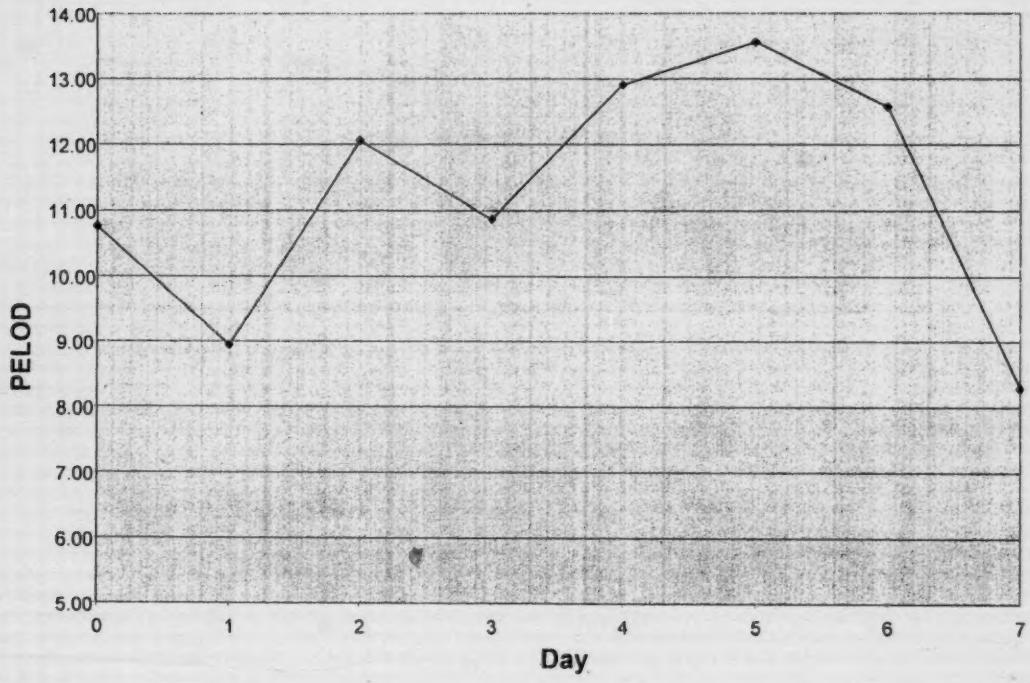
The mean PELOD scores for patients in the PICU were 10.76 (SD = 4.55, median = 12.00, range = 1 to 21) on POD 0, 8.95 (SD = 7.44, median = 11.00, range = 0 to 23) on POD 1, 12.06 (SD = 10.03, median = 11.00, range = 0 to 31) on POD 2, 10.87 (SD = 8.07, median = 11.00, range = 0 to 22) on POD 3, 12.91 (SD = 7.82, median = 12.00, range = 0 to 22) on POD 4, 13.56 (SD = 7.00, median = 12.00, range = 0 to 22) on POD 5, 12.57 (SD = 3.36, median = 12.00, range = 10 to 20) on POD 6, and 8.29 (SD = 5.06, median = 11.00, range = 0 to 12) on POD 7 (figure 7).

There was a strong relation between the PELOD scores and all six thyroid hormone levels, especially with the PM hormone samples. Mixed effect modeling showed evidence of a significant relation between the PELOD scores and the PM

samples of TSH ($p = 0.002$), TT3 ($p = 0.0001$ and 0.002), FT3I ($p = 0.047$ and 0.151), T3U ($p = 0.007$), FT4 ($p = 0.014$) and RT3 ($p = 0.016$). The AM levels of TSH ($p = 0.005$), TT3 ($p = 0.034$ and 0.046), and T3U ($p = 0.006$) including all 21 patients also provided evidence of a significant relation with the PELOD scores. However, excluding identified outliers (patients 12 or 19) for the AM TT3 and TSH models resulted in non-significance.

The best fit relationships between the PELOD scores and the hormones were the natural logarithm for RT3 and FT4, quadratic for FT3I and TT3, and linear for TSH and T3U, regardless of being AM or PM values. The AM TSH and TT3 and PM RT3 and FT4 levels did not concur with regards to model significance or insignificance with all the models explored. However, the best fit or most appropriate models were considered the most accurate and reliable for inclusion in the study results given the model assumptions and fit for the available data. By using mixed models, the random effects incorporated captured all of the observed variability between patients. The interclass correlation coefficient (ICC) values ranged from 0.3136 to 0.4724, suggesting that the correlation between observations for the same patient was strong.

Figure 7: Mean PELOD Score



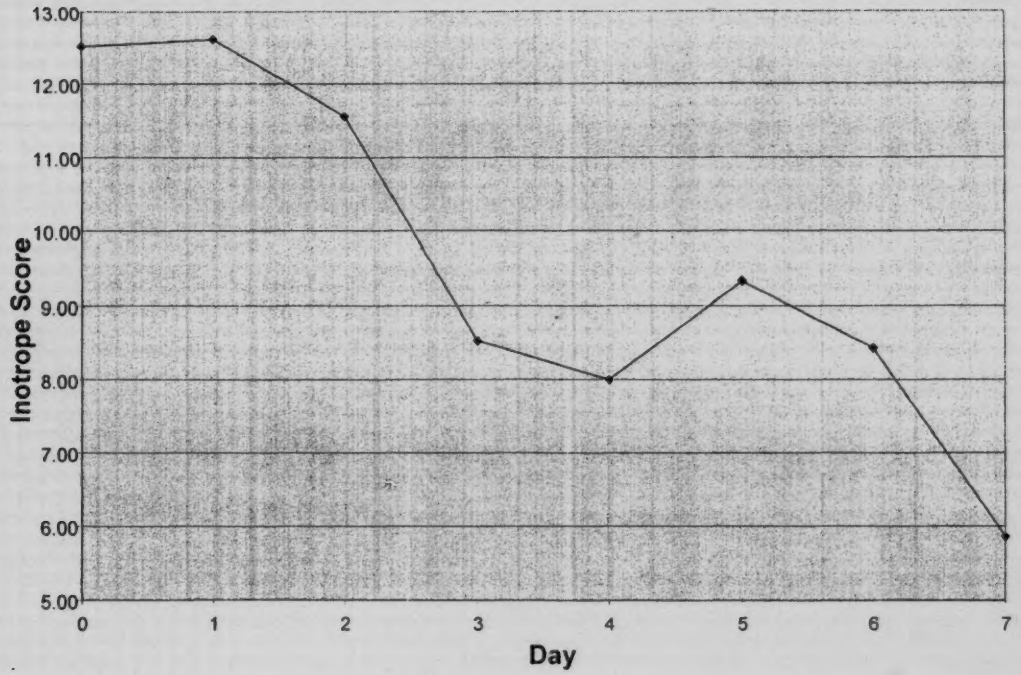
5.4.3 Inotrope Score

The mean inotrope scores for patients in the PICU were 12.52 (SD = 12.69, median = 8, range = 0 to 40) on POD 0, 12.62 (SD = 13.25, median = 8.00, range = 0 to 38) on POD 1, 11.56 (SD = 13.17, median = 4.50, range = 0 to 38) on POD 2, 8.53 (SD = 10.99, median = 0.00, range = 0 to 30) on POD 3, 8.00 (SD = 7.69, median = 7.00, range = 0 to 23) on POD 4, 9.33 (SD = 7.42, median = 10.00, range = 0 to 20) on POD 5, 8.43 (SD = 7.91, median = 8.00, range = 0 to 23) on POD 6, and 5.86 (SD = 7.80, median = 0.00, range = 0 to 19) on POD 7 (figure 8).

Like the PELOD scores, the inotrope scores showed a strong relation to the thyroid hormones. Again, this relation was most evident with the PM samples. Mixed effect modeling showed evidence of a significant relation between the inotrope scores and the PM samples of TSH ($p < 0.0001$), TT3 ($p = 0.001$ and 0.007), FT3I ($p = 0.023$ and 0.045), T3U ($p < 0.0001$), and RT3 ($p = 0.001$). The PM samples of FT4 did not show evidence of a relation with the inotrope scores ($p = 0.433$). For FT3I, there was no evidence of a relationship with the PM levels when an identified outlier (patient 3) was excluded in the analysis. The AM levels of TSH ($p = 0.001$) and T3U ($p < 0.0001$) also showed evidence of a relation with the inotrope scores. There was also evidence of a relationship between the inotrope scores and the AM FT4 levels when identified outliers (patients 3 ($p = 0.047$) and 6 ($p = 0.037$)) were excluded from the analysis.

The best fit relationships between the inotrope scores and the hormones were the natural logarithm for RT3 and FT4, quadratic for FT3I and TT3 and the natural logarithm of inotrope score with a linear function of TSH and T3U, regardless of being AM or PM values. The AM FT3I, FT4 and TSH levels did not concur with regards to model significance or insignificance with all models explored. The same was true for the PM FT3I levels. However, again, the best fit or most appropriate models were considered the most accurate and reliable for inclusion in the study results given the model assumptions and fit for the available data. The ICC values ranged from 0.1239 to 0.5266, suggesting that the correlation between observations for the same patient ranged from relatively weak (e.g. PM TT3) to strong (e.g. PM TSH), depending on the hormone.

Figure 8: Mean Inotrope Score



CHAPTER 6: DISCUSSION

6.0 Study Characteristics

In the first two chapters, this paper provides an extensive review of the available literature on the natural history, pathophysiology, and possible treatment of NTIS in critical illness with a specific emphasis on children undergoing cardiac surgery. The new study outlined in the later chapters adds valuable information to the existing literature. The study's sample size of 21 is amongst the largest of the published pediatric studies and the duration of 8 days of thyroid measurements amongst the longest. In addition, hormone measurements were drawn twice daily for the first 4 days postoperatively in patients that remained in the PICU. This frequent sampling in the extended postoperative period is unique to this study. An average of over 60 thyroid hormone assays was performed on each patient. Finally, to the best of my knowledge, this is only the second study in children undergoing cardiac surgery to compare NTIS changes to a critical illness scoring scale. [3] It is the largest and longest duration study to do so, and the first that I am aware of to use the Pediatric Logistic Organ Dysfunction (PELOD) score [64] for this comparison.

Despite the larger sample size compared to past studies of similar populations, the limitations of this study may include the restrictions that a sample size of 21 has on statistical testing and the resulting statistical inferences. The sample size is smaller at certain time points due to missed collections or insufficient sample

volumes. In addition, the sample size decreases as the duration from surgery increases since some patients were transferred out of the PICU, where twice daily sampling was accomplished, or they were discharged from the hospital altogether. However, while the continued natural history and recovery of the thyroid hormones are important to follow in regards to further understanding the etiology and effects of NTIS, one could argue that the precise thyroid levels in a child well enough to be transferred from the PICU or the hospital have questionable clinical significance. The smaller sample sizes may only pose a possible concern in the subgroup analyses such as when comparing those patients who received dopamine and those that did not. Any concerns about the sample size should be lessened by the similar results provided by both the parametric and nonparametric testing and by the evidence of strong statistical significance, represented by p values, found in many of the statistical tests. In addition, visual inspection of the graphical representations of the data reveals clinically meaningful results.

6.1 Natural History of NTIS

All the children undergoing cardiac bypass surgery for correction of a congenital heart lesion demonstrated the biochemical changes of NTIS. It could be argued that correction for multiple testing, such as the Bonferroni correction, should be considered in the analysis of the thyroid hormone changes. This is a legitimate consideration. Most of the statistical testing would still be significant with this correction. Importantly, the overall pattern of the thyroid hormone changes and the resulting conclusions would not be significantly altered.

The lowest mean TSH level was 0.36 mU/L which was just at the lower limit of the normal range. The lowest mean TT3 level of 0.46 nmol/L was below the lower limit of the normal range. The highest mean RT3 level was 940.07 ng/L which was well above the normal range. In fact, all the postoperative mean RT3 levels were well above the upper range of normal. The lowest mean FT4 level of 7.26 pmol/L and the lowest mean FT3I level of 0.65 were both below the normal ranges. The TSH levels recovered back to preoperative levels on POD 4 with some evidence of a possible rise above the preoperative levels starting on POD 7. The FT4 and arguably the RT3 levels both demonstrated a recovery to preoperative levels, but the TT3, FT3I and T3U showed no evidence of recovery by POD 7.

As outlined in chapter 2, one of the causes of NTIS is thought to be the down regulation of DI and the upregulation of D3. D1 normally converts T4 to T3 and RT3 to T2. D3 converts T4 to RT3 and T3 to T2. The eventual increase and recovery of FT4 and the decrease and recovery of RT3, together with the lack of recovery of TT3 and FT3I may indicate a gradual normalization of the deiodinases with perhaps a quicker normalization of D3 compared to D1.

The decrease of FT4 below normal levels as found in this study is not always a feature of NTIS. In fact, a normal FT4 is considered by some as a classic feature of NTIS. It is more likely that the FT4 level is a reflection of the severity of illness and the degree of NTIS, with more severely ill children demonstrating

more severe NTIS as reflected in decreased FT4 levels in addition to a more prolonged suppression of the T3 hormones. This is consistent with the lack of recovery of the TT3 and FT3I levels by POD 7 in this study paired with the decrease in FT4 levels. The FT4 levels were inversely correlated to some markers of illness severity at certain time points including PICU days, hospital days, and to ventilation days. Admittedly, these correlations were not as consistent as with some of the other hormones. In addition, subgroup analysis showed that the FT4 levels decreased in the patients undergoing the Fontan procedure but did not show evidence of significant changes in the other patients. The subgroup of patients undergoing Fontan procedure also had a greater and more prolonged effect on their T3 hormones. As described later, the Fontan group appears to be more severely ill than the non-Fontan group. This difference in the degree of NTIS has been illustrated in previous studies comparing patients undergoing Fontan procedures to those undergoing other cardiac surgeries. [74]

In contrast to the TT3 and FT3I levels, the T3U levels increased immediately postoperatively and remained above the normal range throughout the study period. As detailed later, these elevated T3U levels were strongly correlated to clinical outcomes. T3U is rarely measured in the previous NTIS studies. One study in adults also found elevated levels of T3U in NTIS. [119] To the best of my knowledge, no previous natural history study in children with NTIS has measured T3U levels. A treatment study in neonates measured T3U but the authors did not provide details of its levels in the publication. [69] T3U reflects the quantity of

unoccupied thyroxine-binding globulin (TBG) and T4-binding prealbumin (TBPA) sites. A higher T3U level indicates less available binding sites. A high T3U level is therefore classically seen in hyperthyroidism as the increased endogenous T4 and T3 hormones bind to the available TBG and TBPA binding sites. However, the increased T3U levels in this study are coupled with decreased TT3, FT3I, and FT4 levels. Therefore, this is likely reflective of decreased levels of TBG and TBPA themselves which would result in lower total, or bound, thyroid hormone levels. It is theoretically not reflective of a binding inhibitor as is implicated in previous studies [24 144], or to decreased binding secondary to severe illness as these should result in elevated free hormone levels, and as mentioned the FT4 and FT3I were both low in the study population. Low levels of TBG and TBPA have been found in a previous study of children undergoing cardiac surgery. [9] However, the low levels were already present preoperatively in that study. TBG levels have also been shown to be low in other examples of acute illness. [98] This is an area that requires further study as little information is available at present.

In contrast to some other studies, the decrease in TSH did not seem to precede the changes in the other thyroid hormones, but rather occurred relatively simultaneously. This was consistent in both the parametric and non parametric testing. These findings would dispute the role of the central suppression of the hypothalamic – pituitary axis as the lone factor in NTIS and implicate another factor in the initial decreases of TT3, FT3I, and FT4. It is possible that the twice

daily sampling did not capture a preceding decrease in TSH. Consistent with other studies the TSH levels did recover earlier than the other hormones. [11 82]

6.2 Correlation of NTIS to Clinical Characteristics and Status

The subgroup analyses performed in this study on those patients that received dopamine or corticosteroid, or underwent the Fontan procedure are limited by their sample sizes but still offer interesting results that can not be discounted.

6.2.1 Dopamine

Dopamine has been shown previously to suppress TSH secretion. [55 132] Subgroup analysis in this study did not show evidence of dopamine affecting the magnitude of the decrease in TSH, or any of the other hormones for that matter. However, dopamine use did result in a more prolonged decrease in TSH with an earlier change from preoperative levels and a later recovery. This was associated with more prolonged NTIS changes in FT4, RT3, TT3, T3U, and FT3I. The prolonged decreases in FT4, TT3, and FT3I found in the dopamine group can physiologically be explained by the prolonged suppression of TSH. Some previous literature has indicated that RT3 is not affected by dopamine. [55 132] Dopamine use has also been shown to not have an effect on deiodinase activity. [101] Therefore, the associated changes in RT3 and T3U are more difficult to explain but may be indicative of sicker patients. The PELOD scores, PICU days, and ventilation days were higher in the patients that received dopamine and

therefore it appears that they were more severely ill than the patients that did not receive dopamine.

6.2.2 Corticosteroids

Corticosteroids are also thought to suppress TSH secretion and therefore exacerbate the changes of NTIS. [17] The number of patients who received corticosteroids in this study was too small to allow for in depth subgroup analysis. However, when the study population was reanalyzed without the patients who received corticosteroids there was a greater recovery in TSH levels with an increase above preoperative levels on POD 7. This would support previous findings that corticosteroids suppress TSH secretion. In addition, the RT3 seemed to recover quicker in the group that did not receive corticosteroids. Therefore when taken in isolation, corticosteroid therapy appears to be detrimental to thyroid function and recovery during critical illness. However, it is also possible that the patients treated with corticosteroids were more severely ill. The small patient numbers did not lend itself to assessing this possibility any further and therefore the results should be interpreted with some caution.

6.2.3 Fontan Procedure

Previous studies have identified more prolonged and a greater degree of NTIS changes in patients undergoing Fontan procedures compared to other surgical repairs of congenital cardiac defects. [74] Like the other subgroup analyses, the analysis of the Fontan versus non Fontan patients is limited in my study by

sample size. In addition, the results should be assessed cautiously as the analysis was a post-hoc exploration. However, the results obtained are similar to previous reports and therefore seem clinically credible.

Both the Fontan and non Fontan groups showed evidence of NTIS but the hormone changes were greater and more prolonged in the Fontan group. The decrease of TT3 and FT4, and the increase in T3U were greater in the Fontan group. The duration of the hormone level changes were also more prolonged. The TT3 and T3U did not return to preoperative levels by POD 7. This is similar to the finding by Mainwaring and colleagues who showed that FT3, TT3, FT4, and TT4 had not returned to baseline by POD 8 in patients undergoing Fontan procedures. [74] However, in contrast, the Mainwaring study showed low TSH levels until POD 8 while this study illustrated recovery of the TSH levels on POD 3. Both studies are quite small and therefore precise conclusions about specific days are difficult to make. However, in general it appears that patients undergoing Fontan procedures develop greater NTIS than other cardiac surgery patients. The contrast of the TSH recovery without recovery of TT3 in this study is difficult to explain. It may be a result of the small sample size, or it could implicate another etiology of the NTIS in this population outside of hypothalamic-pituitary suppression. The increased NTIS changes were associated with increased severity of illness. All the markers of illness severity, including PELOD scores, inotrope scores, PICU days, hospital days, and mechanical ventilation days, were higher in the Fontan group.

6.2.4 CPB and Aortic Clamp Times

There was no evidence that the CPB and aortic clamp times affected the degree of NTIS. Interestingly, this implies that more complicated or prolonged procedures do not worsen the thyroid changes. This is in contrast to some previous studies. [73] [81] [102] The dilutional effects of the bypass solutions have been implicated as causing thyroid changes immediately post operatively. [73] [81] The concentrations of the thyroid hormones in the bypass solutions were not assessed in my study. This would have been an interesting addition to the analysis. However, it is also interesting to ponder how different expertise and practice amongst different centers in regards to the technical administration of the bypass and cross clamp affect the thyroid changes. As surgical practices advance and improve will NTIS improve? Therefore, will newer studies, like this one, demonstrate some different results than older studies?

6.2.5 Surgical Temperature

Intraoperative hypothermia has been shown to result in lower postoperative TSH levels. [102] Others have shown no difference in the postoperative TSH levels but did show the presence of an intraoperative TSH surge with DHCA [105] The levels of the other thyroid hormones did not differ in that study. In my study, while there was no cohort that underwent DHCA, lower temperatures were associated with lower FT3I and TT3 levels on POD 0 but not at later times in the postoperative period. The TSH levels were not related to temperature. On a purely theoretical

basis, if one assumes that cooler temperatures can serve a positive protective role in critical illness, then the lower FT3I and TT3 seen in this study may theoretically be adaptive. However, since there was no DHCA cohort the effect of lower temperatures is difficult, if not impossible, to ascertain in this study.

6.2.6 Weight and Age

Lower preoperative weight was associated with lower FT3I and TT3 levels. This implies that smaller patients develop greater NTIS. This is consistent with previous studies. [73 82 102] However, when the weights are reanalyzed as standard Z-scores for age these correlations are no longer present. Age, however, was correlated to FT3I and TT3 similarly to weight. Therefore, it can be concluded that decreased age, and not weight, is associated with greater NTIS.

It has been suggested that smaller or younger children may be more susceptible to the hemodilutional effects of the CPB solutions. [82] However, in my study the age was associated to later levels and not the immediate postoperative levels. This would suggest that intraoperative hemodiltution is not the causative factor. One could theorize that the younger children may have less mature hypothalamic-pituitary-thyroid axes but then differences in the TSH levels in addition to the other hormones would be expected. It is possible that the younger children showed evidence of greater NTIS changes because they were more severely ill. Age did show correlation to some markers of illness severity including ventilation days, and PELOD and inotrope scores at certain time points.

6.3 Correlation of NTIS to Illness Severity

The correlations of the hormone changes in NTIS to markers of illness severity are discussed below. These correlations suggest the possibility that NTIS may not be an adaptive mechanism. At the very least, NTIS is associated with and a marker of worse clinical outcome and illness severity. While this association does not implicate NTIS as a cause of critical illness, and in fact the inverse may be true, it also does not support its role as preventative and adaptive.

6.3.1 PICU, Hospital, and Mechanical Ventilation Days

Clinical outcomes were strongly related to TT3, FT3I and T3U levels in this study. Greater NTIS changes were correlated to more prolonged hospital stays with increased PICU and mechanical ventilation requirements. The hormone levels on POD 0 in the PM, generally drawn within 6 to 14 hours from the end of surgery, appeared to be predictive of clinical outcome. PICU, hospital and mechanical ventilation days all showed strong positive correlation to the T3U level and inverse correlation to FT3I and TT3 levels on POD 0 in the PM. This was not true for the thyroid measurements done earlier on POD 0, upon arrival to the PICU. Except for T3U, this was also not true for the measurements done after POD 0 until POD 2 and 3. Therefore, the hormone measurements on POD 0 in the PM may be able serve as a valuable clinical tool in predicting the postoperative clinical course. Specifically, all the patients who required prolonged mechanical ventilation, PICU, and hospital days had T3U levels greater than or equal to 0.44

on POD 0 in the PM. In addition, all the patients who required prolonged mechanical ventilation or PICU stays had TT3 levels less than or equal to 0.7 nmol/L at this time point. A patient was 12 times more likely to be in the PICU for 10 or more days if their TT3 level was 0.7 nmol/L or less on POD 0 in the PM. The patients requiring a prolonged hospital stay had slightly higher TT3 levels as a group but they all still had levels less than or equal to 0.9 nmol/L. Hospital days were also inversely correlated to the FT4 levels, and positively correlated to the RT3 levels at POD 0 in the PM. The T3U level itself may be the most valuable marker as illustrated by the fact that all patients with T3U levels greater than or equal to 0.50 at POD 0 in the PM required hospital stays of 21 days or more. A patient was 20 times more likely to be in the hospital for 20 or more days if their T3U level was 0.5 or greater on POD 0 in the PM.

The later thyroid measurements from POD 2 or 3 onwards were also correlated to these clinical outcomes but these correlations later in the postoperative course obviously do not have the same predictive potential. The T3U correlation to clinical outcome was quite robust and even more consistent than that found with TT3 and FT3I.

The correlation to clinical outcome evident early in the postoperative course could theoretically indicate that NTIS changes precede clinical changes. NTIS may be the "chicken before the egg". This is obviously not proof of a causal relation but does provide some credence to the theory that NTIS is maladaptive and worsens

clinical outcome. However, this theory that NTIS changes precede clinical changes is convincingly challenged by the analysis of the PELOD and inotrope scores using mixed effect modeling, as discussed in the next section. The thought that NTIS may be maladaptive is not challenged by this analysis, however. Conversely, one could argue that these are two mutually distinct events. Specifically, one could claim that sicker patients develop worse NTIS and, completely unrelated, sicker patients also have more prolonged and complicated clinical courses.

6.3.2 PELOD and Inotrope Scores

The results of the mixed models showed evidence of significant relations between the thyroid hormones and the PELOD and inotrope scores. These findings are quite thought provoking and provide some unique insight from this study. The relations shown in the mixed models were convincingly more evident with the PM hormone values, compared to the AM, for both the PELOD and inotrope scores. The PELOD and inotrope scores represent a patient's worse clinical status over a 24 hour period, and in this study were measured from midnight to midnight. The models show that the PM thyroid samples, collected around midnight, are significantly related to the clinical status, characterized by the PELOD and inotrope scores, of the preceding 24 hours. Therefore, this could easily suggest that alterations in the level of illness preceded the changes in the thyroid hormones. Illness severity may appear to be the "chicken before the egg".

As outlined by Koch and others, conclusions about causal relations and disease are complex and difficult. [40 84] While this study does not irrefutably outline a cause and effect relationship, it does at least justify further consideration of the theory that illness itself may cause NTIS. The results of the study show strong statistical support of this theory, the temporal relation is supported in the mixed models, it is clinically plausible, and it is supported by other reports. [3] To try to study this theory further, one could design a study to develop and validate a diagnostic rule to predict thyroid function according to an illness severity classification. Such a study would require a large sample size likely necessitating a multi-centered approach. To further distinguish between cause and association would be rather labour intensive. Repeated frequent measures of illness severity and thyroid function would be needed to illustrate that changes to illness severity, both deterioration and improvement, unquestionably preceded any NTIS changes. This cause and effect relationship has been illustrated to some extent in animal models where induction of illness resulted in NTIS. [13]

NTIS seems to be maladaptive, as indicated in the previous section by its association with worse clinical outcomes. The results of the PELOD and inotrope scores analyses suggest that the magnitude of the NTIS changes appears to be a direct consequence of the magnitude of the underlying illness. One can therefore arguably consider that *severe* illness may cause *severe* NTIS.

CHAPTER 7: SUMMARY AND FUTURE DIRECTION

7.0 Summary

This relatively large and lengthy study illustrates that children undergoing cardiac bypass surgery for correction of congenital heart lesions develop NTIS. Some of these biochemical changes are not yet corrected by 8 days following surgery. As opposed to some past studies, the TSH changes did not seem to precede the other thyroid hormone changes. However, TSH levels did recover back to baseline prior to those of the other hormones. Unique to this pediatric study was the finding that T3U levels increase significantly as part of the NTIS changes.

Certain clinical parameters including dopamine use, corticosteroid use, type of surgery, patient's age and weight, and perhaps intraoperative body temperature increased the degree of NTIS. CPB and aortic cross clamp times did not have effects on the extent of NTIS. The degree of the hormone changes in NTIS strongly correlated to clinical outcome and illness severity. Thyroid hormone changes shortly after surgery appeared to be predictive of clinical outcome. Increased illness severity may cause increased NTIS changes.

7.1 Future Direction

This study provides many answers but also provokes many more questions. The T3U changes in this study coupled with the previous study looking at TBG and TBPA levels [9], and the adult study measuring T3U [119], highlight the need to

further study the role of decreased binding proteins in the etiology and possible intervention of NTIS.

The utilization of the early thyroid changes of NTIS as a predictive tool of clinical outcome could also be further investigated. This may prove useful to identify patients requiring further intervention if a therapy is eventually proven to be conclusively beneficial. It could also be a tool to counsel families on the expected clinical course and to plan for hospital bed and resource utilization.

The degree of critical illness severity appears to be linked to NTIS. Therefore, the most affective therapies for NTIS may turn out to be advancements and improvements in surgical and post operative care. Based on the findings of this study and others, certain recommendations could be made in regards to the care of children undergoing cardiac surgery. If possible, the use of dopamine and corticosteroids should be limited. The role of intraoperative temperature needs to be pursued further.

I would recommend that any future study in this area should consider patients undergoing Fontan procedures separate from others, follow patients for longer than 8 days following surgery, and measure binding protein levels. In addition studies in children with critical illnesses other than cardiac surgery are limited and should be considered.

BIBLIOGRAPHY

1. Adriaanse R, Romijn JA, Brabant G, Endert E, Wiersinga WM. Pulsatile thyrotropin secretion in nonthyroidal illness. J Clin Endocrinol Metab 1993; 77:1313-7.

2. Ahima RS, Prabakaran D, Mantzoros C *et al.* Role of leptin in the neuroendocrine response to fasting. Nature 1996; 382:250-2.

3. Allen DB, Dietrich KA, Zimmerman JJ. Thyroid hormone metabolism and level of illness severity in pediatric cardiac surgery patients. J Pediatr 1989; 114:59-62.

4. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000; 283:1038-45.

5. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. J Clin Endocrinol Metab 2006; 91:3725-45.

6. Avenell A, Noble DW, Barr J, Engelhardt T. Selenium supplementation for critically ill adults. Cochrane Database Syst Rev 2004; CD003703.

7. Bartalena L, Martino E, Brandi LS *et al.* Lack of nocturnal serum thyrotropin surge after surgery. J Clin Endocrinol Metab 1990; 70:293-6.

8. Becker RA, Vaughan GM, Ziegler MG *et al.* Hypermetabolic low triiodothyronine syndrome of bum injury. Crit Care Med 1982; 10:870-5.

9. Belgorosky A, Weller G, Chaler E, Iorcansky S, Rivarola MA. Evaluation of serum total

thyroxine and triiodothyronine and their serum fractions in nonthyroidal illness secondary to congenital heart disease. Studies before and after surgery. J Endocrinol Invest 1993; 16:499-503.

10. Bettendorf M, Schmidt KG, Grulich-Henn J, Ulmer HE, Heinrich UE. Tri-iodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study. Lancet 2000; 356:529-34.

11. Bettendorf M , Schmidt KG, Tiefenbacher U, Grulich-Henn J, Heinrich UE, Schonberg DK. Transient secondary hypothyroidism in children after cardiac surgery. Pediatr Res 1997; 41:375-9.

12. Bialkowski J. Use of thyroid hormones after cardiopulmonary bypass in children. Cardiol Young 1998; 8:139-40.

13. Boelen A, Platvoet-ter Schiphorst MC, Bakker O, Wiersinga WM. The role of cytokines in the lipopolysaccharide-induced sick euthyroid syndrome in mice. J Endocrinol 1995; 146:475-83.

14. Boelen A, Platvoet-Ter Schiphorst MC, Wiersinga WM. Association between serum interleukin-6 and serum 3,5,3'-triiodothyronine in nonthyroidal illness. J Clin Endocrinol Metab 1993; 77:1695-9.

15. Boelen A, Platvoet-Ter Schiphorst MC, Wiersinga WM. Soluble cytokine receptors and the low 3,5,3'-triiodothyronine syndrome in patients with nonthyroidal disease. J Clin Endocrinol Metab 1995; 80:971-6.

16. Boelen A, Platvoet-ter Schiphorst MC, Wiersinga WM. Immunoneutralization of

interleukin-1, tumor necrosis factor, interleukin-6 or interferon does not prevent the LPS-induced sick euthyroid syndrome in mice. J Endocrinol 1997; 153:115-22.

17. Brabant G, Brabant A, Ranft U *et al*. Circadian and pulsatile thyrotropin secretion in euthyroid man under the influence of thyroid hormone and glucocorticoid administration. J Clin Endocrinol Metab 1987; 65:83-8.

18. Brabant G, Prank K, Ranft U *et al*. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. J Clin Endocrinol Metab 1990; 70:403-9.

19. Bremner WF, Taylor KM, Baird S *et al*. Hypothalamo-pituitary-thyroid axis function during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1978; 75:392-9.

20. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab 1986; 63:1-8.

21. Brogan TV, Bratton SL, Lynn AM. Thyroid function in infants following cardiac surgery: comparative effects of iodinated and noniodinated topical antiseptics. Crit Care Med 1997; 25:1583-7.

22. Carrel T, Eckstein F, Englberger L, Mury R, Mohacsi P. Thyronin treatment in adult and pediatric heart surgery: clinical experience and review of the literature. Eur J Heart Fail 2002; 4:577-82.

23. Cho YM, Kim MS, Shin CS *et al*. Dynamic change in plasma leptin level during the perioperative period. Horm Res 2003; 59:100-4.

24. Chopra IJ, Solomon DH, Teco GN, Eisenberg JB. An inhibitor of the binding of thyroid hormones to serum proteins is present in extrathyroidal tissues. Science 1982; 215:407-9.

25. Chopra IJ. Clinical review 86: Euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab 1997; 82:329-34.

26. Chowdhury D, Ojamaa K, Parnell VA, McMahon C, Sison CP, Klein I. A prospective randomized clinical study of thyroid hormone treatment after operations for complex congenital heart disease. J Thorac Cardiovasc Surg 2001; 122:1023-5.

27. Chowdhury D, Parnell VA, Ojamaa K, Boxer R, Cooper R, Klein I. Usefulness of triiodothyronine (T3) treatment after surgery for complex congenital heart disease in infants and children. Am J Cardiol 1999; 84:1107-9.

28. Coiro V, Harris A, Goodman HM, Vagenakis A, Braverman L. Effect of pharmacological quantities of infused 3,3',5'-triiodothyronine on thyroxine monodeiodination to 3,5,3'-triiodothyronine. Endocrinology 1980; 106:68-75.

29. Cooper DK, Novitzky D. Invited letter concerning: Changes in plasma-free thyroid hormones during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1992; 104:526-7.

30. Cullen DJ, Civetta JM, Briggs BA, Ferrara LC. Therapeutic intervention scoring system: a method for quantitative comparison of patient care. Crit Care Med 1974; 2:57-60.

31. Davies PH, Black EG, Sheppard MC, Franklyn JA. Relation between serum interleukin-6 and thyroid hormone concentrations in 270 hospital in-patients with non-thyroidal

illness. Clin Endocrinol (Oxf) 1996; 44:199-205.

32. De Groot LJ. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab 1999; 84:151-64.

33. De Jongh FE, Jobsis AC, Elte JW. Thyroid morphology in lethal non-thyroidal illness: a post-mortem study. Eur J Endocrinol 2001; 144:221-6.

34. Debaveye Y, Ellger B, Mebis L *et al.* Tissue deiodinase activity during prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone-releasing peptide-2. Endocrinology 2005; 146:5604-11.

35. den Brinker M, Dumas B, Visser TJ *et al.* Thyroid function and outcome in children who survived meningococcal septic shock. Intensive Care Med 2005; 31:970-6.

36. den Brinker M, Joosten KF, Visser TJ *et al.* Euthyroid sick syndrome in meningococcal sepsis: the impact of peripheral thyroid hormone metabolism and binding proteins. J Clin Endocrinol Metab 2005; 90:5613-20.

37. Dimmick S, Badawi N, Randell T. Thyroid hormone supplementation for the prevention of morbidity and mortality in infants undergoing cardiac surgery. Cochrane Database Syst Rev 2004; CD004220.

38. Dong Q, Hawker F, McWilliam D, Bangah M, Burger H, Handelsman DJ. Circulating immunoreactive inhibin and testosterone levels in men with critical illness. Clin Endocrinol (Oxf) 1992; 36:399-404.

39. Erickson VJ, Cavalieri RR, Rosenberg LL. Thyroxine-5'-deiodinase of rat thyroid, but not

that of liver, is dependent on thyrotropin. Endocrinology 1982; 111:434-40.

40. Evans AS. Causation and disease: the Henle-Koch postulates revisited. Yale J Biol Med 1976; 49:175-95.

41. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab 1997; 82:4032-6.

42. Gonzalez H, Nardi O, Annane D. Relative adrenal failure in the ICU: an identifiable problem requiring treatment. Crit Care Clin 2006; 22:105-18.

43. Gotzsche LS, Flyvbjerg A, Marshall S, Jorgensen KD, Weeke J. The influence of growth hormone and thyroxine on iodothyronine deiodinase activity in the liver, kidney and brown adipose tissue in hypophysectomized rats. Acta Endocrinol (Copenh) 1991; 125:219-26.

44. Gotzsche LS, Weeke J. Changes in plasma free thyroid hormones during cardiopulmonary bypass do not indicate triiodothyronine substitution. J Thorac Cardiovasc Surg 1992; 104:273-7.

45. Greenspan SL, Klibanski A, Schoenfeld D, Ridgway EC. Pulsatile secretion of thyrotropin in man. J Clin Endocrinol Metab 1986; 63:661-8.

46. Haas NA, Camphausen CK. Triiodothyronine in neonatal heart surgery: Looking for an answer. J Thorac Cardiovasc Surg 2006; 131:505-6; author reply 506.

47. Haas NA, Camphausen CK, Kececioglu D. Clinical review: thyroid hormone replacement

in children after cardiac surgery--is it worth a try? Crit Care 2006; 10:213.

48. Hashimoto H, Igarashi N, Yachie A, Miyawaki T, Sato T. The relationship between serum levels of interleukin-6 and thyroid hormone in children with acute respiratory infection. J Clin Endocrinol Metab 1994; 78:288-91.

49. Herndon DN, Barrow RE, Kunkel KR, Broemeling L, Rutan RL. Effects of recombinant human growth hormone on donor-site healing in severely burned children. Ann Surg 1990; 212:424-9; discussion 430-1.

50. Holzer R, Bockenkamp B, Booker P, Newland P, Ciotti G, Pozzi M. The impact of cardiopulmonary bypass on selenium status, thyroid function, and oxidative defense in children. Pediatr Cardiol 2004; 25:522-8.

51. Hulst JM, van Goudoever JB, Visser TJ, Tibboel D, Joosten KF. Hormone levels in children during the first week of ICU-admission: is there an effect of adequate feeding? Clin Nutr 2006; 25:154-62.

52. Ishii H, Inada M, Tanaka K *et al.* Induction of outer and inner ring monodeiodinases in human thyroid gland by thyrotropin. J Clin Endocrinol Metab 1983; 57:500-5.

53. Joosten KF, de Kleijn ED, Westerterp M *et al.* Endocrine and metabolic responses in children with meningoccocal sepsis: striking differences between survivors and nonsurvivors. J Clin Endocrinol Metab 2000; 85:3746-53.

54. Kaplan MM, Utiger RD. Iodothyronine metabolism in rat liver homogenates. J Clin Invest 1978; 61:459-71.

55. Kaptein EM, Spencer CA, Kamiel MB, Nicoloff JT. Prolonged dopamine administration and thyroid hormone economy in normal and critically ill subjects. J Clin Endocrinol Metab 1980; 51:387-93.

56. Kimura T, Kanda T, Kotajima N, Kuwabara A, Fukumura Y, Kobayashi I. Involvement of circulating interleukin-6 and its receptor in the development of euthyroid sick syndrome in patients with acute myocardial infarction. Eur J Endocrinol 2000; 143:179-84.

57. Klemperer JD, Klein I, Gomez M *et al.* Thyroid hormone treatment after coronary-artery bypass surgery. N Engl J Med 1995; 333:1522-7.

58. Klemperer JD, Zelano J, Helm RE *et al.* Triiodothyronine improves left ventricular function without oxygen wasting effects after global hypothermic ischemia. J Thorac Cardiovasc Surg 1995; 109:457-65.

59. Kuiper GG, Kester MH, Peeters RP, Visser TJ. Biochemical mechanisms of thyroid hormone deiodination. Thyroid 2005; 15:787-98.

60. Lalani A, Dhuper S. Thyroid function tests and the pituitary adrenal response in septic shock (abstract). 2004.

61. Larsen PR, Berry MJ. Nutritional and hormonal regulation of thyroid hormone deiodinases. Annu Rev Nutr 1995; 15:323-52.

62. Larsen P, Davies T, Hay I. Thyroid- the thyroid gland. Wilson J, Foster D, Kronenberg H, Larsen P. Williams textbook of endocrinology. Philadelphia, Pennsylvania: W.B. Saunders Company, 1998: 389-515.

63. Legradi G, Emerson CH, Ahima RS, Flier JS, Lechan RM. Leptin prevents fasting-induced suppression of prothyrotropin-releasing hormone messenger ribonucleic acid in neurons of the hypothalamic paraventricular nucleus. Endocrinology 1997; 138:2569-76.

64. Leteurtre S, Martinot A, Duhamel A *et al.* Development of a pediatric multiple organ dysfunction score: use of two strategies. Med Decis Making 1999; 19:399-410.

65. Lim CF, Docter R, Visser TJ *et al.* Inhibition of thyroxine transport into cultured rat hepatocytes by serum of nonuremic critically ill patients: effects of bilirubin and nonesterified fatty acids. J Clin Endocrinol Metab 1993; 76:1165-72.

66. Lim VS, Fang VS, Katz AI, Refetoff S. Thyroid dysfunction in chronic renal failure. A study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. J Clin Invest 1977; 60:522-34.

67. Linder N, Sela B, German B *et al.* Iodine and hypothyroidism in neonates with congenital heart disease. Arch Dis Child Fetal Neonatal Ed 1997; 77:F239-40.

68. Lynch BA, Brown DM, Herrington C, Braunlin E. Thyroid dysfunction after pediatric cardiac surgery. The Journal of Thoracic Cardiovascular Surgery 2004; 127:1509-11.

69. Mackie AS, Booth KL, Newburger JW *et al.* A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. J Thorac Cardiovasc Surg 2005; 130:810-6.

70. Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR. Type 2 iodothyronine deiodinase is

the major source of plasma T3 in euthyroid humans. J Clin Invest 2005; 115:2524-33.

71. Mainwaring RD, Capparelli E, Schell K, Acosta M, Nelson JC. Pharmacokinetic evaluation of triiodothyronine supplementation in children after modified Fontan procedure. Circulation 2000; 101:1423-9.

72. Mainwaring RD, Healy RM, Meier FA, Nelson JC, Norwood WI. Reduction in levels of triiodothyronine following the first stage of the Norwood reconstruction for hypoplastic left heart syndrome. Cardiol Young 2001; 11:295-300.

73. Mainwaring RD, Lamberti JJ, Billman GF, Nelson JC. Suppression of the pituitary thyroid axis after cardiopulmonary bypass in the neonate. Ann Thorac Surg 1994; 58:1078-82.

74. Mainwaring RD, Lamberti JJ, Carter TL Jr, Nelson JC. Reduction in triiodothyronine levels following modified Fontan procedure. J Card Surg 1994; 9:322-31.

75. Mainwaring RD, Lamberti J.J. , Nelson JC, Billman G.F. , Carter T.L. , Schell K.H. Effects of triiodothyronine supplementation following modified Fontan procedure. Cardiol Young 1997; 7:194-200.

76. Mainwaring RD, Nelson JC. Thyroid function after cardiopulmonary bypass in neonates [Reply to]. Ann Thorac Surg 1995; 60:745-7.

77. Mainwaring RD, Nelson JC. Supplementation of thyroid hormone in children undergoing cardiac surgery. Cardiol Young 2001; 12:211-7.

78. Maturlo SJ, Rosenbaum RL, Pan C, Surks MI. Variable thyrotropin response to thyrotropin-releasing hormone after small decreases in plasma free thyroid hormone concentrations in patients with nonthyroidal diseases. J Clin Invest 1980; 66:451-6.

79. McMahon CK, Klein I, Ojamaa K. Interleukin-6 and thyroid hormone metabolism in pediatric cardiac surgery patients. Thyroid 2003; 13:301-4.

80. Mebis L, Langouche L, Visser TJ, Van den Berghe G. The Type II Iodothyronine Deiodinase is Upregulated in Skeletal Muscle During Prolonged Critical Illness. J Clin Endocrinol Metab 2007.

81. Mitchell IM. Thyroid function after cardiopulmonary bypass in neonates. Ann Thorac Surg 1995; 60:745-7.

82. Mitchell IM, Pollock JC, Jamieson MP, Donaghey SF, Paton RD, Logan RW. The effects of cardiopulmonary bypass on thyroid function in infants weighing less than five kilograms. J Thorac Cardiovasc Surg 1992; 103:800-5.

83. Modan-Moses D, Ehrlich S, Kanety H *et al.* Circulating leptin and the perioperative neuroendocrinological stress response after pediatric cardiac surgery. Crit Care Med 2001; 29:2377-82.

84. Morabia A. Epidemiological causality. Hist Philos Life Sci 2005; 27:365-79.

85. Mullis-Jansson SL, Argenziano M, Corwin S *et al.* A randomized double-blind study of the effect of triiodothyronine on cardiac function and morbidity after coronary bypass surgery. J Thorac Cardiovasc Surg 1999; 117:1128-34.

86. Mungan N, Yildizdas D, Topaloglu K, Yuksel B, Ozer G. Thyroid hormone levels and their relations to survival in children with bacterial sepsis and septic shock (abstract). 2004.

87. Murzi B, Iervasi G, Masini S *et al.* Thyroid hormones homeostasis in pediatric patients during and after cardiopulmonary bypass. Ann Thorac Surg 1995; 59:481-5.

88. Noel GL, Suh HK, Stone JG, Frantz AG. Human prolactin and growth hormone release during surgery and other conditions of stress. J Clin Endocrinol Metab 1972; 35:840-51.

89. Novitzky D, Cooper DK, Barton CI *et al.* Triiodothyronine as an inotropic agent after open heart surgery. J Thorac Cardiovasc Surg 1989; 98:972-7; discussion 977-8.

90. Novitzky D, Cooper DK, Swanepoel A. Inotropic effect of triiodothyronine (T3) in low cardiac output following cardioplegic arrest and cardiopulmonary bypass: an initial experience in patients undergoing open heart surgery. Eur J Cardiothorac Surg 1989; 3:140-5.

91. Novitzky D, Human PA, Cooper DK. Inotropic effect of triiodothyronine following myocardial ischemia and cardiopulmonary bypass: an experimental study in pigs. Ann Thorac Surg 1988; 45:50-5.

92. Novitzky D, Human PA, Cooper DK. Effect of triiodothyronine (T3) on myocardial high energy phosphates and lactate after ischemia and cardiopulmonary bypass. An experimental study in baboons. J Thorac Cardiovasc Surg 1988; 96:600-7.

93. Osborn DA. Thyroid hormones for preventing neurodevelopmental impairment in preterm

infants. Cochrane Database Syst Rev 2001; CD001070.

94. Osborn DA, Hunt RW. Postnatal thyroid hormones for preterm infants with transient hypothyroxinaemia. Cochrane Database Syst Rev 2007; CD005945.

95. Osborn DA, Hunt RW. Postnatal thyroid hormones for respiratory distress syndrome in preterm infants. Cochrane Database Syst Rev 2007; CD005946.

96. Osborn DA, Hunt RW. Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2007; CD005948.

97. Pagliacci MC, Pelicci G, Grignani F *et al.* Thyroid function tests in patients undergoing maintenance dialysis: characterization of the 'low-T4 syndrome' in subjects on regular hemodialysis and continuous ambulatory peritoneal dialysis. Nephron 1987; 46:225-30.

98. Pannall PR, Fuller WR, Peisach AR *et al.* Thyroxine-binding globulin concentrations in the plasma of severely ill patients. Clin Chem 1980; 26:1925-6.

99. Peeters RP, Kester MH, Wouters PJ *et al.* Increased thyroxine sulfate levels in critically ill patients as a result of a decreased hepatic type I deiodinase activity. J Clin Endocrinol Metab 2005; 90:6460-5.

100. Peeters RP, van der Geyten S, Wouters PJ *et al.* Tissue thyroid hormone levels in critical illness. J Clin Endocrinol Metab 2005; 90:6498-507.

101. Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced

activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab 2003; 88:3202-11.

102. Plumpton K, Haas NA. Identifying infants at risk of marked thyroid suppression post-cardiopulmonary bypass. Intensive Care Med 2005; 31:581-7.

103. Portman MA, Fearneyhough C, Karl TR *et al.* The Triiodothyronine for Infants and Children Undergoing Cardiopulmonary Bypass (TRICC) study: design and rationale. Am Heart J 2004; 148:393-8.

104. Portman MA, Fearneyhough C, Ning XH, Duncan BW, Rosenthal GL, Lupinetti FM. Triiodothyronine repletion in infants during cardiopulmonary bypass for congenital heart disease. J Thorac Cardiovasc Surg 2000; 120:604-8.

105. Ririe DG, Butterworth JF, Hines M, Hammon JW Jr, Zaloga GP. Effects of cardiopulmonary bypass and deep hypothermic circulatory arrest on the thyroid axis during and after repair of congenital heart defects: preservation by deep hypothermia? Anesth Analg 1998; 87:543-8.

106. Robuschi G, Medici D, Fesani F *et al.* Cardiopulmonary bypass: a low T4 and T3 syndrome with blunted thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH). Horm Res 1986; 23:151-8.

107. Romijn JA, Adriaanse R, Brabant G, Prank K, Endert E, Wiersinga WM. Pulsatile secretion of thyrotropin during fasting: a decrease of thyrotropin pulse amplitude. J Clin Endocrinol Metab 1990; 70:1631-6.

108. Romijn JA, Wiersinga WM. Decreased nocturnal surge of thyrotropin in nonthyroidal

illness. J Clin Endocrinol Metab 1990; 70:35-42.

109. Rosen D, Serafini M, Phillips L, Steiner M, Ashton C, Gustafson R. Thyroid hormone for children with cardiac failure (abstract). Crit Care Med 1996; 24:A154.

110. Ross OC, Petros A. The sick euthyroid syndrome in paediatric cardiac surgery patients. Intensive Care Med 2001; 27:1124-32.

111. Ross R, Miell J, Freeman E *et al.* Critically ill patients have high basal growth hormone levels with attenuated oscillatory activity associated with low levels of insulin-like growth factor-I. Clin Endocrinol (Oxf) 1991; 35:47-54.

112. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med 1995; 23:78-83.

113. Saatvedt K, Lindberg H, Geiran OR *et al.* Thyroid function during and after cardiopulmonary bypass in children. Acta Anaesthesiol Scand 1998; 42:1100-3.

114. Saberi M, Utiger RD. Augmentation of thyrotropin responses to thyrotropin-releasing hormone following small decreases in serum thyroid hormone concentrations. J Clin Endocrinol Metab 1975; 40:435-41.

115. Shangraw RE, Jahoor F, Miyoshi H *et al.* Differentiation between septic and postburn insulin resistance. Metabolism 1989; 38:983-9.

116. Shigematsu H, Smith RA, Shatney CH. Detrimental effect of reverse triiodothyronine in hemorrhagic shock. Crit Care Med 1987; 15:933-8.

117. Shulkin BL, Utiger RD. Reverse triiodothyronine does not alter pituitary-thyroid function in normal subjects. J Clin Endocrinol Metab 1984; 58:1184-7.

118. Simpson J, Williams FL, Delahunty C *et al.* Serum thyroid hormones in preterm infants and relationships to indices of severity of intercurrent illness. J Clin Endocrinol Metab 2005; 90:1271-9.

119. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 1981; 245:43-5.

120. Snyder PJ, Utiger RD. Inhibition of thyrotropin response to thyrotropin-releasing hormone by small quantities of thyroid hormones. J Clin Invest 1972; 51:2077-84.

121. Span LF, Hermus AR, Bartelink AK *et al.* Adrenocortical function: an indicator of severity of disease and survival in chronic critically ill patients. Intensive Care Med 1992; 18:93-6.

122. Spencer C, Eigen A, Shen D *et al.* Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem 1987; 33:1391-6.

123. Stathatos N , Levetan C, Burman KD, Wartofsky L. The controversy of the treatment of critically ill patients with thyroid hormone. Best Practice and Research Clinical Endocrinology and Metabolism 2001; 15:465-78.

124. Stouthard JM, van der Poll T, Endert E *et al.* Effects of acute and chronic interleukin-6 administration on thyroid hormone metabolism in humans. J Clin Endocrinol Metab 1994; 79:1342-6.

125. Takala J, Ruokonen E, Webster NR *et al.* Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999; 341:785-92.

126. Thorner M, Vance M, Laws Jr E, Horvath E, Kovacs K. Hypothalamus and pituitary - the anterior pituitary. Wilson J, Foster D, Kronenberg H, Larsen P. Williams textbook of endocrinology. Philadelphia, Pennsylvania: W.B Saunders Company, 1998: 249-340.

127. Uzel N, Neyzi O. Thyroid function in critically ill infants with infections. Pediatr Infect Dis 1986; 5:516-9.

128. Vagenakis AG, Rapoport B, Azizi F, Portnay GI, Braverman LE, Ingbar SH. Hyperresponse to thyrotropin-releasing hormone accompanying small decreases in serum thyroid hormone concentrations. J Clin Invest 1974; 54:913-8.

129. Van den Berghe G, Baxter RC, Weekers F *et al.* The combined administration of GH-releasing peptide-2 (GHRP-2), TRH and GnRH to men with prolonged critical illness evokes superior endocrine and metabolic effects compared to treatment with GHRP-2 alone. Clin Endocrinol (Oxf) 2002; 56:655-69.

130. Van den Berghe G, de Zegher F, Baxter RC *et al.* Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. J Clin Endocrinol Metab 1998; 83:309-19.

131. Van den Berghe G, de Zegher F, Bouillon R. Clinical review 95: Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 1998; 83:1827-34.

132. Van den Berghe G, de Zegher F, Lauwers P. Dopamine and the sick euthyroid syndrome in critical illness. Clin Endocrinol (Oxf) 1994; 41:731-7.

133. Van den Berghe G, de Zegher F, Lauwers P, Veldhuis JD. Luteinizing hormone secretion and hypoandrogenaemia in critically ill men: effect of dopamine. Clin Endocrinol (Oxf) 1994; 41:563-9.

134. Van den Berghe G, Wouters P, Weekers F *et al.* Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. J Clin Endocrinol Metab 1999; 84:1311-23.

135. Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. European Journal of Endocrinology 2000; 143:1-13.

136. Van den Berghe G. The neuroendocrine response to stress is a dynamic process. Best Practice and Research Clinical Endocrinology and Metabolism 2001; 15:405-19.

137. van der Poll T, Romijn JA, Wiersinga WM, Sauerwein HP. Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man. J Clin Endocrinol Metab 1990; 71:1567-72.

138. Vermes I, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. J Clin Endocrinol Metab 1995; 80:1238-42.

139. Voerman BJ, Strack van Schijndel RJ, Groeneveld AB, de Boer H, Nauta JP, Thijs LG.

Effects of human growth hormone in critically ill nonseptic patients: results from a prospective, randomized, placebo-controlled trial. Crit Care Med 1995; 23:665-73.

140. Voerman HJ, Strack van Schijndel RJ, de Boer H, van der Veen EA, Thijs LG. Growth hormone: secretion and administration in catabolic adult patients, with emphasis on the critically ill patient. Neth J Med 1992; 41:229-44.

141. Voerman HJ, van Schijndel RJ, Groeneveld AB *et al*. Effects of recombinant human growth hormone in patients with severe sepsis. Ann Surg 1992; 216:648-55.

142. Walker JD, Crawford FA Jr, Spinale FG. 3,5,3' Triiodo-L-thyronine pretreatment with cardioplegic arrest and chronic left ventricular dysfunction. Ann Thorac Surg 1995; 60:292-9.

143. Wang C, Chan V, Tse TF, Yeung RT. Effect of acute myocardial infarction on pituitary-testicular function. Clin Endocrinol (Oxf) 1978; 9:249-53.

144. Wilcox RB, Nelson JC, Tomei RT. Heterogeneity in affinities of serum proteins for thyroxine among patients with non-thyroidal illness as indicated by the serum free thyroxine response to serum dilution. Eur J Endocrinol 1994; 131:9-13.

145. Wolfe RR. Substrate utilization/insulin resistance in sepsis/trauma. Baillieres Clin Endocrinol Metab 1997; 11:645-57.

146. Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M. Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 1985; 60:444-50.

147. Yu J, Koenig RJ. Regulation of hepatocyte thyroxine 5'-deiodinase by T3 and nuclear receptor coactivators as a model of the sick euthyroid syndrome. J Biol Chem 2000; 275:38296-301.

148. Zucker AR, Chernow B, Fields AI, Hung W, Burman KD. Thyroid function in critically ill children. J Pediatr 1985; 107:552-4.